

# *The American Journal of* **DIGESTIVE DISEASES**

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**DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION**

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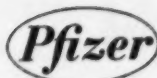
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1. Dumas, K. J.; Carlazzi, M., and Wright, W. A.: Antibiotic Med. J 296 (May) 1955. 2. Prigot, A.: Ann. New York Acad. Sc., in press. 3. Milberg, M. B., and Michael, M., Jr.: Ibid. 4. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Prepared in Collaboration with the Committee on Therapeutic Nutrition, Food and Nutrition Board, National Research Council, Washington, D. C., 1952.

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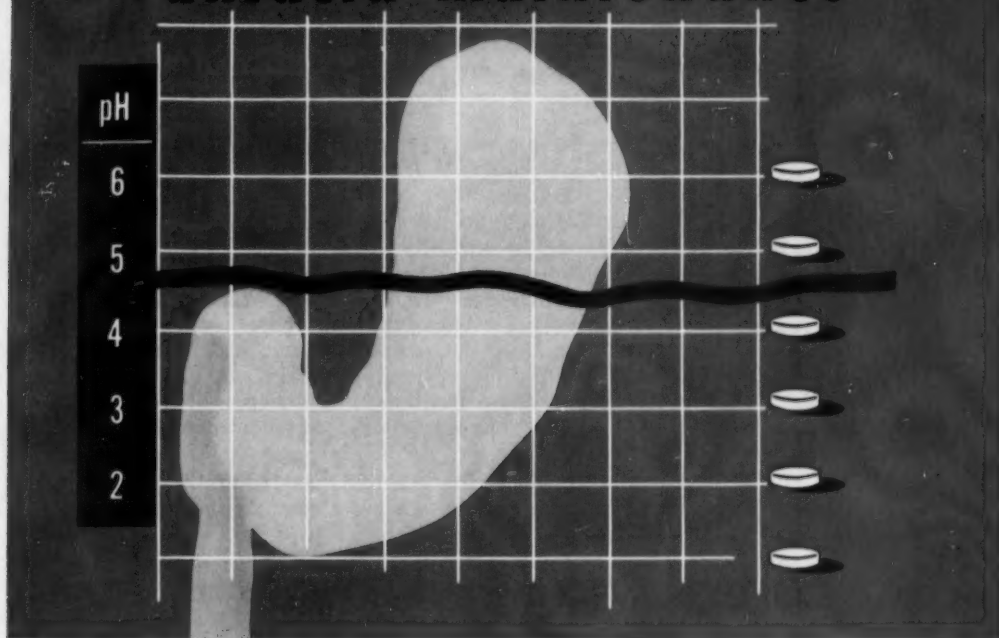
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\*Cannon, P. R.; Frazier, L. E., and Hughes, R. H.: Factors Influencing Amino Acid Utilization in Tissue Protein Synthesis, in Symposium on Protein Metabolism, New York, The National Vitamin Foundation, Inc., 1954, pp. 55-90.

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## ANTIBIOTICS AND ANTIBIOTIC COMBINATIONS IN AMEBIASIS

HARRY SENECA, M. D., M. S. (MED.), F.A.C.P., New York, N. Y.

TEN YEARS ago, Hargreaves (1) published a classical paper on the treatment of amebiasis with penicillin, and thus opened a new chapter in the treatment of parasitic infections with antibiotics. He treated 57 cases of resistant amebiasis with penicillin, and observed that within 24 hours, the patients became asymptomatic and the stools were formed within 48 hours, but they continued to pass amebas in their stools. Following the treatment with penicillin or sulfasuxidine, the resistant cases became amenable to the conventional antiamebic treatment. Apparently penicillin controlled the secondary bacterial invaders of the lesions, which are probably responsible for the intestinal as well as the constitutional symptoms, but had no effect on *Endameba histolytica*. Once the bacterial infection or inflammation was under control, it is conceivable that the antiamebic drugs became available to the amebas in adequate concentrations, or/and the amebas became more susceptible to the drugs.

Knoll and Howell (2) reported that penicillin had no effect on the cysts and cultures of *E. histolytica* in 5,000 to 10,000 Oxford units/ml. Shaffer and Frye (3) grew *E. histolytica* in the presence of bacterial extracts, 950 Oxford units/ml penicillin and 1,500 ug/ml streptomycin for 100 subcultures. Seneca, Henderson and Harvey (4) observed that penicillin or streptomycin was not inhibitory to *E. histolytica* in 1,000 units or ug per ml. A combination of the two, in equal concentrations killed or inhibited the ameba in the first generation, in 2,000 units ug/ml, and in the second generation in 1,000 units ug/ml. Such penicillin levels can not be attained in the mucosa of the colon when the antibiotic is administered parenterally, moreover it is unlikely that such levels can be reached if it is given by mouth, because the rate of penicillin absorption or permeation is very variable, and penicillinase inactivates the antibiotic before it is absorbed.

McVay, Laird and Sprunt (5, 6) in 1949 introduced the antibacterial and antiamebic treatment of intestinal amebiasis by using the broad spectrum antibiotic chlortetracycline. Their results were so dramatic that the management of intestinal amebiasis was revolutionized because the antibiotic therapy has practically replaced the conventional and respected antiamebic drugs such as the halogenated compounds (chiniofon, vioform, diodoquin), arsenicals (carbarsone, acetarsone, treparsol, thiocarbarsone, arsthinol etc), bismuth compounds, and restricted the use of emetine in specific cases of hepatic complications.

For the present, the antibiotic therapy of hepatic amebiasis has been a failure. Chloroquin is the standard therapeutic agent. Conan (7) recommended 0.6 gm of the base (1.0 gm of chloroquin diphosphate) daily for two days, followed by 0.3 gm (0.5 gm of diphos-

phate) daily for two to three weeks. Basmuevo and Gutierrez Erstali (8) used 0.01 gm of the salt per pound up to 100 pounds body weight daily for three days, followed by 0.01 gm per pound up to 50 pounds body weight daily for 24 days. Emmett (9) used 0.5 gm daily doses. Four of seven of Sodeman et al (10) patients recovered promptly with chloroquin, but in the remaining three, either the dose of chloroquin was doubled, or chloroquin therapy was repeated, or surgical drainage or emetine had to be used simultaneously. The effectiveness of chloroquin in hepatic amebiasis may not be efficacious without other procedures, as is true with emetine.

### OXYTETRACYCLINE

As of the writing of this paper, the drug of choice in the treatment of amebiasis is oxytetracycline or Terramycin. Publications by Most and Van Assendelft (11), Ruiz-Sanchez et al (12), Tobie et al (13), Killough and Magill (14, 48), Elsdon-Dew et al (15), Frye et al (16), Martin et al (17), Sodeman et al (18), McHardy and Frye (19) etc. confirm the effectiveness of oxytetracycline in intestinal amebiasis. Various dosage schemes have been used. The minimum dose was two grams a day for a week, but the recommended dose is two grams initially, followed by two grams a day for ten days, with a total dose of 22 grams.

Tobie et al (13) reported 100 per cent cures, while Frye et al (16) obtained 97.5 per cent cures, and McHardy and Frye (19) averaged 8.5 per cent failures among 435 treated cases.

The question of resistance of *E. histolytica* to oxytetracycline is of great importance in therapy. Shaffer and Washington (20) could not induce resistance to oxytetracycline, chlortetracycline and emetine in two strains of *E. histolytica* after 38 serial transfers in the presence of these drugs. Seneca and Murphy (21) and Seneca (22) cultured eleven strains from various parts of the world in 0.05 to 1.0 ug/ml oxytetracycline from 28 to 51 generations. Eight strains showed no change, two strains became more sensitive and one strain became more resistant. The sensitive strains reverted back to normal sensitivity while the resistant strain maintained its resistance after 10 to 20 subcultures or transfers in the medium in the absence of the antibiotic.

### TETRACYCLINE

Seneca and Bergendahl (23) observed that the antiamebic spectrum of tetracycline was similar to that of oxytetracycline. It was inhibitory to cultures of *E. histolytica* in 62.5 to 250 ug/ml concentration. Seneca (24) treated twenty patients who had colonic amebiasis with 1.5 grams daily for eight days, the total dose was 12 to 15 grams of tetracycline. Nineteen were cured, but the twentieth patient had to discontinue the medication because of severe intestinal side effects such as severe diarrhea and anal pruritus. Additional trials are necessary for the evaluation of the parent member of the tetracycline group.

College of Physicians and Surgeons, Columbia University, New York, New York.

Submitted Mar. 22, 1955.

## CHLORTETRACYCLINE

Since the original observations of McVay et al (5,6) on the effectiveness of chlortetracycline in amebiasis, numerous reports have appeared in the literature on the role of chlortetracycline in amebiasis by Waldo (25), MacDonald (26), Hughes (27), Armstrong et al (28), Gutch (29), Hall (30), Conn (31), Siguier et al (32), Calero (33), Crosnier et al (34), Halwani et al (35), Bordes et al (36), Shookoff and Sterman (37), Radke (38), Tobie et al (13), Elsdon-Dew et al (15), Frye et al (16), Martin et al (17), McHardy and Frye (19) etc. The dose used by these investigators was similar to that of oxytetracycline. In McVay et al's (5,6) series, of 37 patients, 36 were improved, but in four, *E. histolytica* appeared in the stools. Armstrong et al (28) treated 52 patients with very good initial results, but one month after the treatment, seven of 27 cases who were reexamined had *E. histolytica* in their stools. Tobie et al (13) reported 60 per cent effectiveness for chlortetracycline, Frye et al (16) obtained 70.7 per cent effectiveness, while McHardy and Frye (19) averaged 16.6 per cent failures among 697 treated patients. Watts and Vandegrift (39) reported a slight rise in resistance in two strains of *E. histolytica* to chlortetracycline.

## FUMAGILLIN

McCowen et al (40) reported a direct amebicidal effect in 1 in 130 million dilution by fumagillin on cultures of *E. histolytica*, but it was devoid of antibacterial and antifungal effect. Hrenoff and Nakamura (41) confirmed the direct antiamebic effect on *E. histolytica* with *Trypanosoma cruzi* cultures. Clinical evaluation of fumagillin in amebiasis by Anderson et al (42), Anderson (43), Killough and Magill (48), McHardy et al (44), Killough et al (45), McHardy (46), Anderson et al (47) and McHardy and Frye (19) revealed that it was highly effective in the intestinal manifestation of the disease. Although 200 mg daily doses were used initially, there is general agreement that 20 mg three times daily for ten days is probably the effective and safe dose. Killough and Magill (48) treated 67 patients in Egypt with daily dose of 5 to 200 mg, and noted recurrence in 32 patients. It is very difficult to rule out reinfection because of the unhygienic conditions which prevail in Egypt, particularly among the farmers, accordingly some of these cases could be reinfection. McHardy et al (44) and McHardy (46) treated 228 patients with 20 mg three times daily for ten days. Fifty-nine were followed up for 12 months with only six recurrences. McHardy and Frye (19) summarized their results as follows: "Fumagillin has survived enthusiasm in adequate evaluation period and is confirmed as an efficient innocuous amebicidal agent if there is

adherence to the recommended dose levels. A recurrence incidence recorded with fumagillin, as with other therapeutic agents, indicated its limitation and confirms an opinion expressed in 1945 that no one drug is always a successful and complete amebicide." They reported a failure rate of 14 per cent among 119 patients treated with fumagillin.

## CARBOMYCIN

Seneca and Ides (49) observed that carbomycin (Magnamycin) possessed inhibitory effect on *E. histolytica* cultures. The clinical results obtained by Sode-man and Jung (50) and Seneca (51,52) were very promising with one failure in 21 patients treated with carbomycin. As a matter of fact, a patient who was refractory to oxytetracycline, responded to carbomycin therapy. McHardy (46) treated 16 patients and stated that four were intractable and three had recurrence, but admitted that his findings were not conclusive, and that probably the drug was not given the proper trial. Halwani (53) informed the author that carbomycin gave satisfactory results in his cases. The recommended dose was two grams a day for ten days. This antibiotic should be given more extensive clinical trials in intestinal amebiasis.

## CHLORAMPHENICOL

This is a broad spectrum antibiotic, but is not a member of the tetracycline family, and is a nitrobenzene derivative. Conn (31) and Coronel (54) observed favorable results. Frye et al (16) treated 39 patients using 2 grams initially followed by two grams a day for ten days, and reported 53.5 per cent cures. Martin et al (17) observed cures in 11 of 41 patients treated with chloramphenicol, and the failures subsequently responded to other drugs. McHardy and Frye (19) averaged their results in 72 patients treated with this antibiotic and obtained 73.6 per cent failure. Investigations with this antibiotic have been discontinued because of too many failures and toxicity.

## ERYTHROMYCIN

McCowen et al (55) reported that erythromycin (Ilotycin) with an antibacterial spectrum similar to that of penicillin had inhibitory effect on cultures of *E. histolytica*, and was curative in the experimental amebiasis of the rodent. Anderson et al (47) observed that erythromycin was essentially antibacterial, without any direct effect against *E. histolytica*, yet they reported that it was inhibitory in 1 to 5,000 against *E. histolytica* with t organism and 1 to 1,000 against *E. histolytica* with *Trypanosoma cruzi*. In 25 to 200 mg daily doses, none of the 11 monkeys infected were cleared of ameba. Seventeen children were treated with 300 mg daily doses for 14 days with two recurrences. The mean

TABLE I. THE EFFECT OF BACITRACIN, POLYMYXIN B AND BACITRACIN PLUS POLYMYXIN ON CULTURES OF *E. HISTOLYTICA*.

Antibiotic	Korea 1	Columbia	Gloria	No. 517
Polymyxin B	< 1,000 units	1,000 units	1,000 units	1,000 units
Bacitracin	1,000 units	1,000 units	1,000 units	1,000 units
Polymyxin B	125 units	250 units	500 units	125 units
+	+	+	+	+
Bacitracin	125 units	250 units	500 units	125 units

These numbers represent the minimum inhibitory concentration of the antibiotic per ml.



weight of these children was 22 kg. It is apparent that 300 mg for 22 kg is not an adequate or therapeutic dose, because the dose of erythromycin in the usual bacterial infections is the same as is the dose for the tetracycline group. If these children were given twice the dose, probably the cure rate would have been higher. McHardy and Frye (19) considered erythromycin as an adjunctive to the other drugs, at least for the time being.

#### BACITRACIN

Most et al (56,57) treated 51 patients with amebiasis varying in severity from asymptomatic to fulminating dysentery with bacitracin with daily dose of 40 to 120,000 units for a period of 5 to 20 days, but the recommended dose was 80,000 units daily for ten days. In eight acute cases, there was one relapse after eight months, and in three additional patients, parasite relapse occurred 5, 18 and 350 days after therapy. In one case bacitracin was effective after other antiamebic drugs had failed. Of 43 asymptomatic cases, the apparent cure rate was 80 per cent, and the probable cure from one course of bacitracin was 66 per cent. McHardy and Frye (19) tabulated their observation with bacitracin in 205 patients with 31.2 per cent failure. It is thus apparent that bacitracin is a fairly active drug in amebiasis, and probably in combination with other drugs may improve the cure rate in amebiasis. The interest in bacitracin should be kept alive, since there is no absorption of this drug from the gastrointestinal tract, and if combined with another nonabsorbable antibiotic, may exert synergism without giving rise to blood or tissue levels.

#### NEOMYCIN

McVay et al (58) used neomycin in 1952 in intestinal amebiasis. Anderson et al (47) reported that it was inhibitory to cultures of *E. histolytica* with organism t or *Trypanosoma cruzi* in 1 to 1,000. In monkeys in 200 mg/kg, it cleared 5 of 8 monkeys infected with *E. histolytica*, but in 100 mg/kg dose, it failed to clear the infection. In human amebiasis it had 40 per cent efficacy in a group of ten patients. McHardy and Frye (19) considered neomycin as an adjunctive to the treatment, and totaled 63.6 per cent failure among 22 patients.

#### ANISOMYCIN

Lynch et al (59) and Seneca and Bergendahl (60) observed that anisomycin (Flagecidin) was inhibitory to cultures of *E. histolytica* in 2.5 ug/ml concentration. McHardy (61) treated 12 patients with 20 mg three times daily with five recurrences. He is presently using enteric coated tablets and is using larger doses. Since this drug may have toxic side effects, larger doses may not be safe.

#### ANTIBIOTIC SYNERGISM

In vitro synergism was demonstrated by Seneca et al (4) in 1949 by a combination of equal amounts of penicillin + streptomycin. Watt and Vandegrift (39) observed that 2.5 mg/ml polymyxin D inhibited *E. histolytica* in the first subculture, 1 mg/ml in the fourth, 0.9 mg/ml in the fifth and 0.8 mg/ml in the sixth subculture. Circulin inhibited the same culture in 2.5 mg/ml in the first subculture, 1.0 mg/ml in the fourth and 0.9 mg/ml in the sixth subculture. Equal quantities of polymyxin D + circulin (0.35 mg + 0.35 mg) inhibited the culture in the first subculture, and 0.30 mg of polymyxin D + 0.30 mg of circulin inhibited the culture in the second subculture. They concluded that combined polymyxin D and circulin, each of which possessed a low amebicidal action, manifested a synergistic effect and became moderately amebicidal. Anderson et al (47) reported that fumagillin was inhibitory to *E. histolytica* with organism t in 1 to 8 million and *E. histolytica* with *Trypanosoma cruzi* in 1 to 4 to 1 to 16 million. Erythromycin was inhibitory to the two types in 1 to 5,000 and 1 to 1,000 respectively. Fumagillin + erythromycin was inhibitory to the two cultures in 1 to 10 million (fumagillin) + 1 to 10,000 (erythromycin) and 1 to 32 million (fumagillin) + 1 to 1,000 (erythromycin) respectively. Neomycin was inhibitory to both types in 1 to 1,000. Fumagillin + neomycin was inhibitory to the two types in 1 to 40 million (fumagillin) + 1 to 5,000 (neomycin) and 1 to 100 million (fumagillin) + 1 to 4,000 (neomycin) respectively. These data indicated that there was definite synergism in fumagillin + erythromycin and fumagillin + neomycin combinations. In the experimental amebiasis of the monkey, fumagillin cleared 12/19, erythromycin 0/11 and neomycin 5/8, while fumagillin + erythromycin cleared 5/7 and fumagillin + neomycin 5/5, indicating synergism. In the treatment of 38 children in a mental hospital who had 52 separate episodes of infection with *E. histolytica*, fumagillin failed to clear 14 episodes, erythromycin failed in 2 of 17 and fumagillin + erythromycin failed in five of 21 episodes, showing that there was enhancement in the therapeutic effect in fumagillin + erythromycin combination as far as fumagillin effect was concerned, but erythromycin effect was somewhat depressed. It is hard to draw conclusions with small series of patients, and extensive trial should be undertaken clinically.

Synergism was demonstrated by Seneca and Bergendahl (23) in tetracycline + oxytetracycline, and tetracycline group + carbomycin. Oxytetracycline inhibited six strains of *E. histolytica* in 31.25 to 250 ug/ml, and tetracycline inhibited the same strains in 62.5 to 250 ug/ml. There was a four fold increase in the inhibitory effect on the cultures when equal amounts (by weight)

TABLE II. THE EFFECT OF NEOMYCIN, POLYMYXIN B AND NEOMYCIN PLUS POLYMYXIN ON CULTURES OF *E. HISTOLYTICA*.

Antibiotic	Korea 1	Columbia	Gloria	No. 517
Neomycin	500 ug	250 ug	125 ug	500 ug
Polymyxin B	1,000 units	500 units	500 units	500 units
Neomycin	62.5 ug	31.25 ug	31.25 ug	31.25 ug
+	+	+	+	+
Polymyxin	62.5 units	31.25 units	31.25 units	31.25 units

These numbers represent the minimum inhibitory concentration of the antibiotic per ml.

of tetracycline and oxytetracycline were combined, and a two fold increase when tetracycline or oxytetracycline was combined with carbomycin. We have treated a dozen patients using ten grams of oxytetracycline and ten grams of carbomycin, and have observed no failures. Loughlin and Mullin (62) obtained better clinical response when oxytetracycline + carbomycin was used.

The present studies were undertaken to extend the observations on the synergistic effect of antibiotic combinations on cultures of *E. histolytica*.

Bacitracin, polymyxin, tetracycline and oxytetracycline used in these experiments were of the highest purity, and were sterile parenteral forms destined for clinical use.

#### BACITRACIN + POLYMYXIN COMBINATION

Bacitracin, polymyxin and equal amounts of bacitracin + polymyxin were serially diluted from 1,000 to 31.25 units/ml in the 5 ml buffer saline overlay of Boeck Drbohlav egg medium. Sterile starch (rice) was then added, and 25,000 trophozoites of 48 hour old culture of four different strains of *E. histolytica* were then added to each tube. After 48 hours incubation at 37° C, the contents were examined under the low and high powers of the microscope for the presence or absence of growth.

#### NEOMYCIN + POLYMYXIN COMBINATION

Neomycin, polymyxin and neomycin + polymyxin combination were serially diluted in the buffer saline overlay of the egg medium from 1,000 ug or units to 31.25 ug or units per ml. Rice starch and 25,000 trophozoites of ameba were then added, and the tubes were incubated. At the end of 48 hours, the contents were examined microscopically.

#### ANISOMYCIN + TETRACYCLINE OR OXYTETRACYCLINE COMBINATION

Tetracycline or oxytetracycline HCl was serially diluted in the buffer saline overlay of the medium from 800 to 6.25 ug/ml concentration. Sterile anisomycin was serially diluted in 20 to 0.15 ug/ml concentration. Anisomycin + tetracycline or oxytetracycline were combined in 1 to 20 ratio. Ten ug anisomycin + 200 ug broad spectrum per ml were serially diluted to 0.15

ug anisomycin + 3.125 ug broad spectrum per ml. After the addition of rice starch and 25,000 trophozoites from four strains of *E. histolytica*, the tubes were incubated, and the contents were examined microscopically.

#### RESULTS

Table I shows in a tabular form the effect of bacitracin, polymyxin and bacitracin + polymyxin on cultures of *E. histolytica*. Bacitracin inhibited all four strains in 1,000 units/ml, and polymyxin inhibited three strains in 1,000 units per ml, but did not inhibit Korea 1 strain in this concentration. Equal amounts of bacitracin + polymyxin inhibited two strains in 125 units each (250 units combined), a four fold enhancement; one strain in 250 units each (500 units combined), a two fold enhancement; and had no effect on Gloria strain since 500 units each (1,000 units combined) were needed for inhibition.

Table II shows in a tabular form the effect of neomycin, polymyxin and neomycin + polymyxin combination on cultures of *E. histolytica*. Neomycin inhibited one strain in 125 ug/ml, another strain in 250 ug/ml and two other strains in 500 ug/ml concentrations. Polymyxin inhibited three strains in 500 units/ml and Korea 1 strain in 1,000 units/ml. Equal amounts of neomycin + polymyxin inhibited three strains in 31.25 ug neomycin + 31.25 units polymyxin per ml (62.5 ug or/and units per ml), which is a two to eight fold enhancement or synergism. Korea 1 strain was inhibited in 62.5 ug neomycin + 62.5 units polymyxin per ml (125 ug or/and units per ml) which is four to eight fold synergism.

Table III shows the effect of tetracycline, oxytetracycline, anisomycin, tetracycline + anisomycin and oxytetracycline + anisomycin on cultures of *E. histolytica*. Anisomycin inhibited all four strains in 2.5 ug/ml. Tetracycline inhibited three strains in 25 ug/ml and strain 517 in 100 ug/ml. Oxytetracycline inhibited one strain in 25 ug/ml, two strains in 50 ug/ml and one strain in 100 ug/ml concentrations. Anisomycin + tetracycline combination in 1 to 20 ratio, inhibited two strains in 0.31 ug anisomycin + 6.25 ug tetracycline per ml and the other two strains in 0.62 ug anisomycin + 12.5 ug tetracycline per ml, indicating that there was two to 16 fold enhancement for tetracycline and 4 to 8 fold enhancement for anisomycin. Anisomycin + oxytetracycline combination in 1 to 20 ratio inhibited one

TABLE III. THE EFFECT OF TETRACYCLINE, OXYTETRACYCLINE, ANISOMYCIN, AND TETRACYCLINE OR OXYTETRACYCLINE PLUS ANISOMYCIN ON CULTURES OF *E. HISTOLYTICA*

Antibiotic	Korea 1	Columbia	Gloria	No. 517
Tetracycline	25.0 ug	25.0 ug	25.0 ug	100.0 ug
Oxytetracycline	100.0 ug	50.0 ug	50.0 ug	25.0 ug
Anisomycin	2.5 ug	2.5 ug	2.5 ug	2.5 ug
Tetracycline + Anisomycin	12.5 ug + 0.62 ug	12.5 ug + 0.62 ug	6.25 ug + 0.31 ug	6.25 ug + 0.31 ug
Oxytetracycline + Anisomycin	50.0 ug + 2.5 ug	12.5 ug + 0.62 ug	12.5 ug + 0.62 ug	6.25 ug + 0.31 ug

These numbers represent the minimum inhibitory concentration of the antibiotic per ml.

strain in 2.5 ug anisomycin + 50 ug oxytetracycline, two strains in 0.62 ug anisomycin + 12.5 ug oxytetracycline and a fourth strain in 0.31 ug anisomycin + 6.25 ug oxytetracycline per ml, which was two to four fold enhancement for oxytetracycline and 0 to 8 fold increase for anisomycin.

### DISCUSSION

The secondary bacterial infection or inflammation of the amebic lesions of the colon by the bacterial associates in the intestine, plays a very significant role in the pathology of amebiasis. A complete therapeutic weapon

ing the antibiotic treatment. Killough and Magill (48) reported two of 16 patients who received oxytetracycline treatment developed hepatic abscess. Thirteen patients who were receiving fumagillin also developed hepatic abscess. Erythromycin and carbomycin are inhibitory to *E. histolytica* in 200 to 400 ug/ml. These fantastic levels can not be attained in the liver, unless vast quantities are injected intravenously, which may become toxic.

McHardy and Frye (19) give the following tabulation concerning the present status of the antibiotics in the treatment of intestinal amebiasis:

Antibiotic	No. of Patients	No. of Recurrences	Failures
Oxytetracycline	435	37	8.5%
Fumagillin	119	28	14.0%
Chlortetracycline	697	116	16.6%
Bacitracin	205	65	31.2%
Neomycin	22	14	63.6%
Chloramphenicol	72	53	73.6%

Sufficient data for carbomycin, erythromycin and anisomycin are not yet available.

in intestinal phase should possess both antiamebic and antibacterial properties. Such an ideal drug has not yet been discovered, therefore there is a constant need for research and investigation to improve the therapy of amebiasis. There is no single drug which cures all cases of amebiasis, nevertheless, we have patients who have amebiasis and need to be treated. We should use the best available drug or drugs at our disposal, and expect a steady improvement in the therapy of amebiasis.

The classical amebicides such as the halogenated derivatives (chiniofon, diodoquin and vioform), arsenicals (carbarsone, milibis, thioarsenites, arsthinol), aminoquinolines (cloroquin phosphate) and emetine are still in use despite the fact that the antibiotic therapy is more efficacious. The general trend in the past few years has been to intensify research in the antibiotic field. There is no doubt that chloroquin is the drug of choice in the management of hepatic amebiasis, and antibiotic therapy has been a failure in this phase of the disease. Probably the reason why tetracycline group is ineffective is because adequate concentrations of these drugs, in amebicidal concentrations can not be attained in the liver. The inhibitory range of tetracycline drugs against various strains of *E. histolytica* is 25 to 250 ug/ml. Following the maximum oral dose (2 grams), the highest blood level is about 6 ug/ml of serum. In case more than two grams is given, the blood level does not rise. The liver concentrates these drugs, and they are secreted or excreted in the bile, but levels which are amebicidal can not be attained by the oral method of administration. It is possible to get higher blood and tissue levels when the drugs are given by intravenous infusion. Here again amebicidal levels probably can not be maintained long enough to kill the amebas. It is claimed that tetracycline gives higher tissue and blood levels than its derivatives, however the mean blood levels among a large number of individuals show that all three tetracyclines have approximately the same levels in the body (63,64). If a few amebas are already in the portal system and have reached the liver, they may be able to give rise to hepatic complications despite the fact that the patient is receiv-

The defects of an antiamebic antibiotic can be corrected, and/or improved by combining it with another antibiotic. Synergism has been demonstrated in penicillin + streptomycin (4), polymyxin D + circulin (39), tetracycline + oxytetracycline or combination of either with carbomycin (23), fumagillin + erythromycin or fumagillin + neomycin (47). The data presented in this paper indicate that synergism exists in polymyxin + neomycin, polymyxin + bacitracin, tetracycline + anisomycin, and oxytetracycline + anisomycin. A combination of oxytetracycline or tetracycline + fumagillin may probably manifest better synergism against *E. histolytica*, because the former are very potent antibacterial and antiamebic antibiotics, while the latter is the most potent amebicidal agent in vitro, being inhibitory in 1 to 130 million concentration (40), and is a proven therapeutic drug.

A very important complication in the treatment of bacterial infections is the evolution of antibiotic resistant strains of bacteria. As the microorganism comes in constant contact with the antibiotic, it is either killed, or progressively becomes more resistant. The longer the organism is exposed, the greater is the chance of becoming resistant, in other words, we have more resistance to penicillin than against the more recent antibiotics. Chlortetracycline (39) and oxytetracycline (21, 22) resistant strains of *E. histolytica* have been produced in the laboratory. Recurrences following the treatment with antibiotics is a known fact. As more and more antibiotics will be used in the treatment of amebiasis, there may result increased resistance on the part of the ameba to the antibiotic used. Therefore, there should be a keen interest in research to introduce newer drugs or antibiotics to meet this new challenge.

A factor of economic importance in the treatment of amebiasis is the higher cost of the tetracycline group of drugs. Since amebiasis is more prevalent in the poorer countries, the cost of treating a patient may be such that the physician may be obliged to use the cheaper drugs. Side effects of the antibiotics tetracycline group



used in the treatment of intestinal amebiasis are few and not serious. Among the lesser important are nausea, vomiting and diarrhea, but once in a while some of the patients may develop anal pruritus. Most of these can be avoided by taking the drugs on full stomach, or by combining them with cultured butter milk, or yogurt. Yogurt is superior to other types of fermented milk because it contains *Lactobacillus bulgaricus*, *Streptococcus acidilactis* and *Thermobacterium yoghurtii* and also possesses bactericidal properties (65). Very rarely a type of enterocolitis may develop or superimposed infection with *Candida albicans*, *Micrococcus pyogenes aureus*, *Proteus* or *Pseudomonas aeruginosa* may result from the unopposed overgrowth of these bacteria. This is a serious complication, and therefore the drug should be discontinued. The patient should be given erythromycin or carbomycin in case of *M. aureus*, and even sulfadiazine. Polymyxin should be given in case the infection is caused by *Proteus* or *Pseudomonas aeruginosa*. The fluid electrolyte relationship should be restored by giving infusions of saline or glucose. Hydrocortisone ointment is recommended for pruritus.

The side effect of fumagillin are vertigo, anorexia, dermatitis, nausea, vomiting, abdominal cramps, diarrhea, desquamation of the hands, perianal pruritus and even post therapeutic leucopenia with depression of the bone marrow (19,48). Fortunately the present therapeutic dose of 20 mg three times daily gives rise to very few side effects.

Chloramphenicol has practically no gastrointestinal side effects. Unfortunately it is liable to give rise to leucopenia, granulocytopenia, thrombocytopenia, depression of the bone marrow and aplastic anemia. Erythromycin and carbomycin have very minor side effects such as nausea, vomiting and occasional diarrhea. Bacitracin, polymyxin and neomycin are practically non-toxic when given by mouth, but the parenteral method of administration may result in nephrotoxicity with all, liver damage with bacitracin, and neurotoxicity with polymyxin and neomycin.

#### SUMMARY AND CONCLUSION

##### I. Antibiotic synergism on *Endameba histolytica*:

1. Equal amounts by weight of bacitracin + polymyxin exert 0 to 4 fold synergism.
2. Equal amounts by weight of neomycin + polymyxin exert 2 to 8 fold synergism.
3. One to 20 ratio of anisomycin + tetracycline exerts 2 to 16 fold synergism for oxytetracycline and 4 to 8 fold for anisomycin.
4. One to 20 ratio of anisomycin + oxytetracycline exerts 2 to 4 fold synergism for oxytetracycline and 0 to 8 fold synergism.

##### II. A review of the literature revealed that:

1. Oxytetracycline is the drug of choice in amebiasis, and fumagillin is the next in line.
2. Resistance of *E. histolytica* was reported to chlo and oxy-tetracycline.
3. Antibiotic synergism was reported against *E. histolytica* in polymyxin + circulin, tetracycline + oxytetracycline, tetracycline or oxy-

tetracycline + carbomycin, fumagillin + erythromycin or neomycin combinations.

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## THE NORMAL ILEO-CECAL VALVE

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THE roentgenological study of the ileo-cecal region has been the subject of interest to several investigators. An excellent basic contribution to the knowledge of the ileo-cecal valve was made by Fleischner and Bernstein (1) and thus far no other studies have thrown better light along those fundamental anatomical lines. Hinkel (2) has drawn attention toward evaluating the variations in the roentgenological appearance of the ileo-cecal valve as observed in the barium enema studies of the colon and warned against urging unnecessary surgical exploration in the presence of a conspicuous filling defect in this region.

Hinkel's studies were performed by means of the barium clyster. We have approached this subject by attempting to correlate the appearance obtained by barium enema with that noted by means of the oral administration of barium. In turn, roentgenograms of the barium filled anatomical specimens were compared with the clinical roentgenograms. In the individual ambiguous case the combined study by barium enema and the oral administration of barium has been the decisive factor in final evaluation.

This entire subject deserves special emphasis in order to assist the clinician to recognize the manifold varia-



Fig. 1b. Specimen roentgenogram showing an identical picture.



Fig. 1a. Normal appearance of the medially inserted ileo-cecal valve as seen in the barium enema examination. Note both lips and the linear frenal defect extending laterally.



Fig. 1c. Same specimen rotated 90 degrees.

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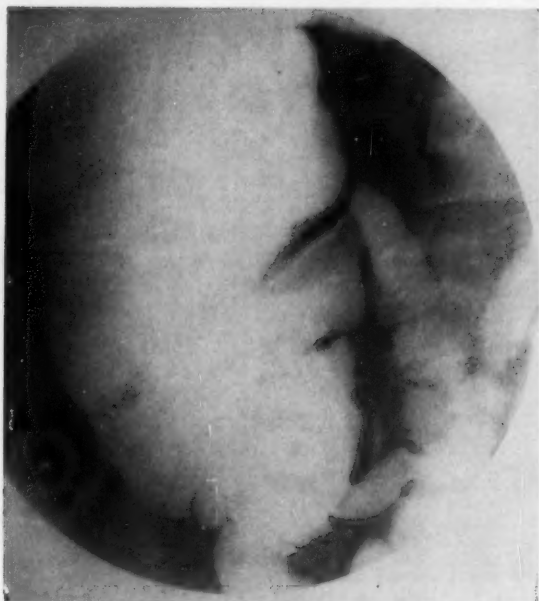


Fig. 2a. Normal ileo-cecal valve.

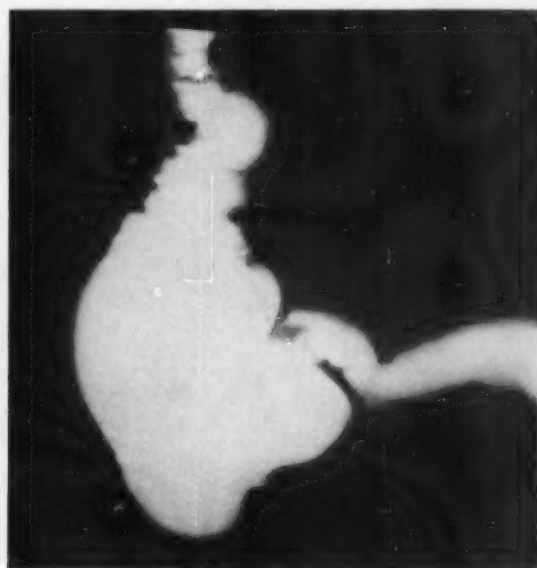


Fig. 2b. Specimen sectional roentgenograms.

tions of the ileo-cecal valve in health and disease. It must be stressed, that just as in the pyloro-duodenal region, normalcy is not a fixed static picture. A knowledge of the morphological variability of the ileo-cecal region is helpful not only in the recognition of the normal from the abnormal, but also in classifying the abnormal status, when it is present.

The ileo-cecal valve fulfills its function by means of its structural anatomy as well as a physiological sphincteric mechanism. The sphincteric action is innervated from the 9th to 12th thoracic nerves, and the 1st and 2nd lumbar segments of the splanchnic nerve, mediated through the intramural plexus of Auerbach. The frequency of contraction varies in normal individuals in the periods of contraction and relaxation. Various physiological states influence the tonus of the valve.

The anatomical structure affords an actual valvular action. There is a sudden anatomical transition with the small calibre ileum becoming the large calibre cecum. There is a corresponding change in the mucosa, in accordance with the abrupt physiological change from absorption to storage and excretion. Likewise the muscular anatomy changes suddenly adapting itself to the need of an actual valvular mechanism. As the lower end of the ileum enters the cecum obliquely, the invaginated portion of the cecal wall forms two transverse folds or lips, one above the other, with a central slit-like opening. The lips fuse laterally to produce a crescentic fold on either side of the ileo-cecal orifice called the frenula of the valve, which are continued around the interior of the cecum (Fig. I-IV). Lasser and Rigler (3) in



Fig. 2c. Photograph of same specimen.

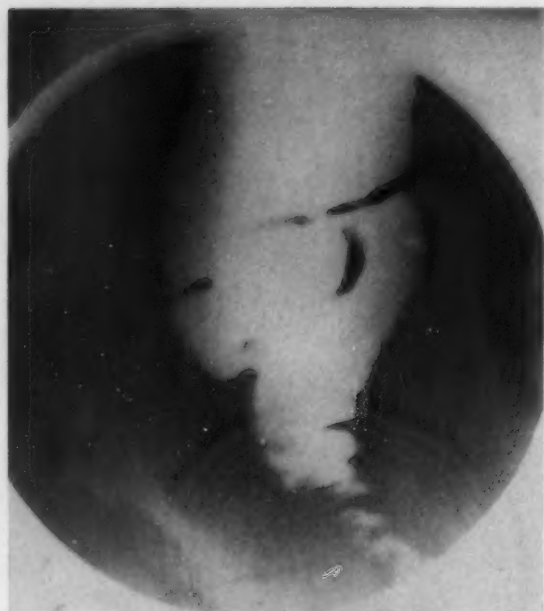


Fig. 3a. Normal ileo-cecal valve.



Fig. 3b. Specimen roentgenogram illustrating similar defect.

their studies of the valvular action of the valve conclude that the structural characteristics cause the upper lip to assume a passive role in the process of closure of the valve in a distended colon, while the lower lip assumes a mobile active part.

#### TECHNIQUE OF ROENTGENOLOGICAL STUDY

Our studies of the ileo-cecal valve in the normal living have been derived from observations of this region during double contrast barium enemata, supplemented when necessary by the oral administration of barium. During barium enema fluoroscopy the flow of barium is maintained by gravity until ileo-cecal incompetency is obtained. Spot films are then taken without and with compression. The defect caused by the valve is occasionally well visualized without compression, but usually it is obscured by overdistention with barium. Pressure films are essential for detailed study, even though they exaggerate the filling defect. With a normal medial insertion of the valve a simple supine exposure is sufficient. At times the ileum appears on the medial aspect of the cecum, but the valve is not displayed on simple supine compression. Under such circumstances, the patient must be rotated into an appropriate oblique position (usually left posterior or right anterior oblique). In other words, a posteriorly inserted

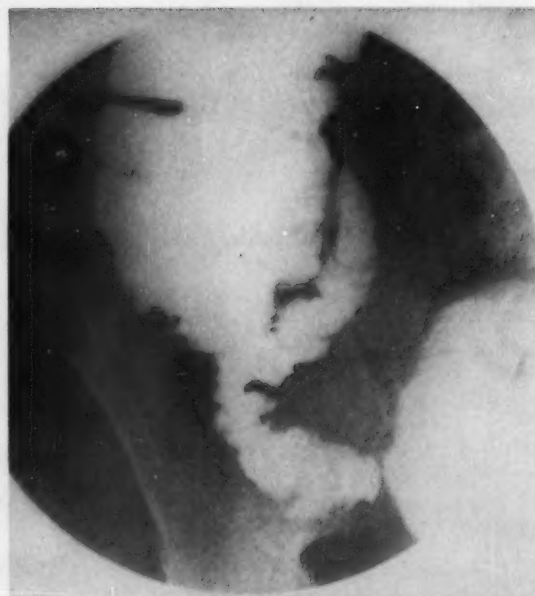
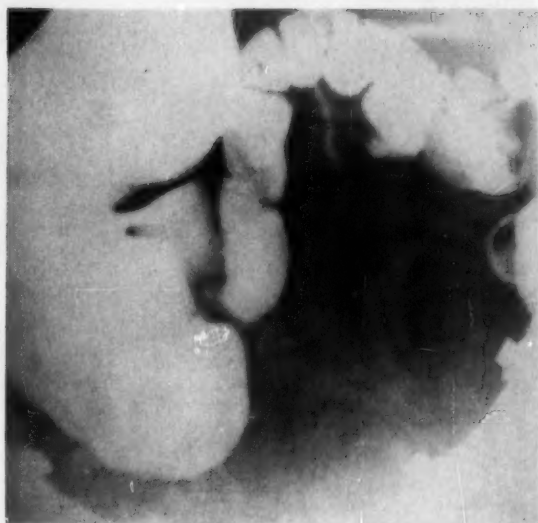
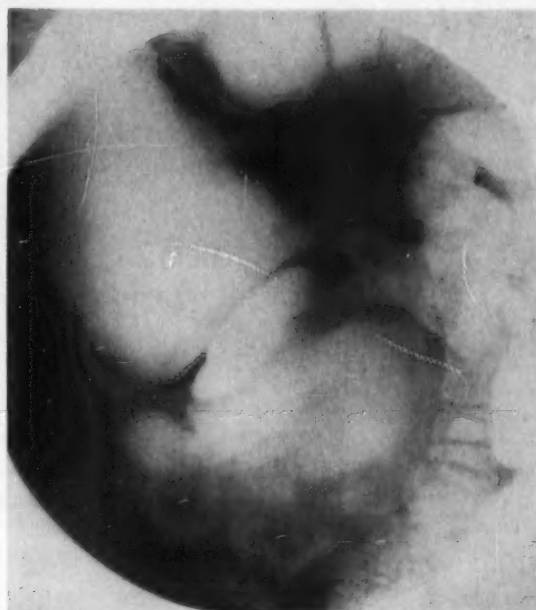


Fig. 3c. Normal ileo-cecal valve. Note stellate appearance of the ileum at the orifice.





4a



4b



4c



4d

Fig. 4. Variations in appearance of the ileo-cecal valve of 4 different cases.

valve will be observed en face on supine compression, but in profile in the oblique posture. A mobile cecum may therefore present different appearances of the ileo-cecal valve in various positions.

The barium enema contrast study helps to define the valve with greater accuracy, and actually delineates the contours within the cecal lumen. Therefore, whenever the ileo-cecal region is suspect, an air contrast study is essential.

At times a questionable filling defect in the cecum may tax one's ingenuity even after a thorough air study. A differential diagnosis of a normal or a hypertrophied valve from an abnormal filling defect (neoplastic or inflammatory) may be quite difficult. Under such circumstances the patient is examined by meal by mouth. The appearance of the ileo-cecal valve, thus obtained, is compared with the appearance by barium enema. The greater familiarity an examiner has with this procedure, the less likely will he have to resort to exploratory laparotomy for the final answer. Indeed as greater confidence in the correct diagnosis is attained, the radiologist will feel more secure in preventing unnecessary surgery.

In order to support and confirm our observations made from the clinical roentgenograms, we took several autopsy specimens of the ileo-cecal region and



Fig. 5. En face view of a posteriorly inserted ileo-cecal valve.



Fig. 6a. En face view of a posteriorly inserted ileo-cecal valve.

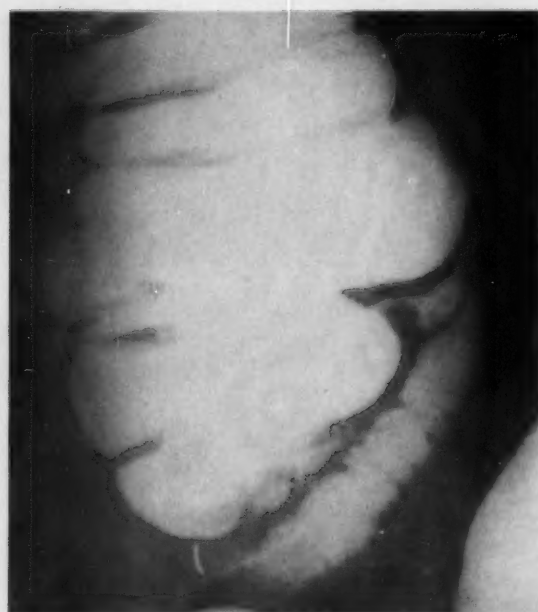


Fig. 6b. Same case rotated in the left posterior oblique illustrating the profile view.

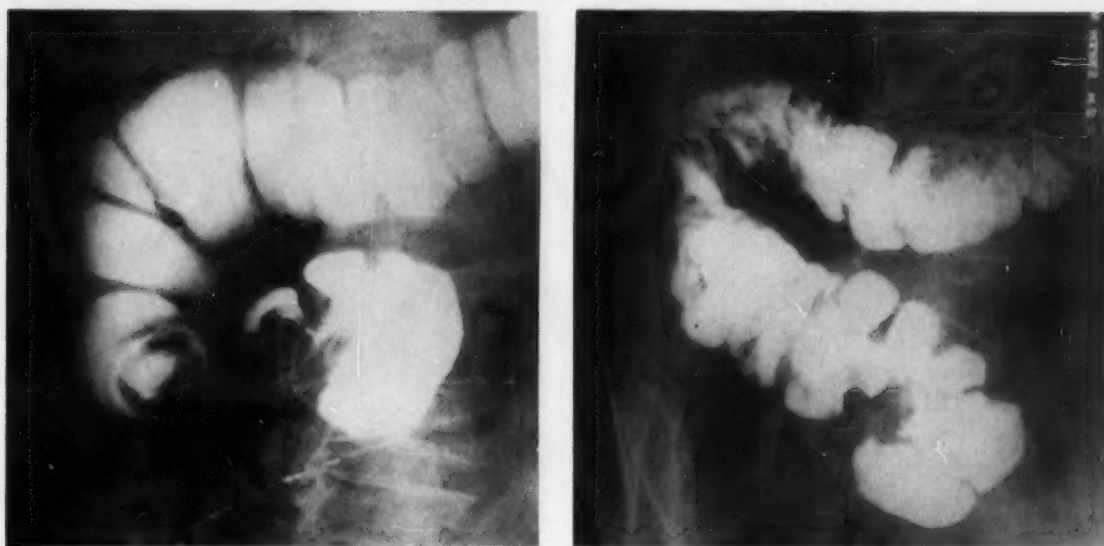


Fig. 7a & b. Two separate barium enema examinations illustrating a large defect on the lateral posterior aspect of a mobile cecum.

studied the valve after filling with barium. At times the impression of the ileo-cecal valve was not obvious in the roentgenograms of the specimens due to overdistention, which necessitated a study utilizing laminography. It is very gratifying to note that the specimen roentgenograms are identical to the clinical roentgenograms.

In the autopsy specimens which were filled with



Fig. 7c. Examination by meal by mouth in the left posterior oblique proving that the defect represents the ileo-cecal valve. Note the entrance of the terminal ileum. This demonstration convinced the surgeon not to operate.

barium for roentgenological studies the following findings were noted repeatedly. When the ascending colon was closed by suture and the cecum filled from the terminal ileum, there was no difficulty in filling the cecum. On the other hand, when the terminal ileum is closed and the cecum was filled from the ascending colon, the terminal ileum did not fill until the colon was distended to a marked degree. As the specimens under study did not constitute a large number, as no exact measurements of the pressure gradients on either side were made, and as the dynamic factors working in the physiological living as opposed to dead anatomical specimens are myriad, it is not justifiable to draw any definite conclusions with regard to the hydrodynamic function of the ileo-cecal valve. However, it reaffirms the fact that, under normal conditions the major function of the ileo-cecal valve is to prevent the reflux of cecal contents into the ileum, although it plays a minor role in regulating the transition of ileal contents into the cecum. As the cecum distends the frena are stretched. They pull upon the lips from either side drawing them firmly together. Thus the valve can stand high pressure in the cecum but yields to a relatively low pressure from the ileum.

#### NORMAL ROENTGENOLOGICAL APPEARANCE

The ileo-cecal valve is usually visualized roentgenographically on the medial aspect of the cecum when observed in an antero-posterior projection. In an average case it appears as two clear cut radiolucent bands in the barium filled colon due to the impression caused by the two lips of the valve. Frequently the filling defect caused by the upper lip extends far beyond the edge of the lip almost to the lateral wall of the colon merging with the thin thread like filling defect caused by the frenulum. This linear radiolucent defect (which is really circumferential) extends from the valve proper and presents a characteristic appearance that is diag-



Fig. 8. Lateral insertion of the ileo-cecal valve: (a) barium enema; (b) meal by mouth

nostic (see Figures I to V). When it is accentuated it acts as a sphincter, the sphincter of Varioli (Fig. IX). This sphincteric action is the reason why the terminal ileum may be filled by barium enema before the entire colon.

There is a central thin and elongated triangular collection of barium in between the two radiolucent defects corresponding to the ileo-cecal orifice which is continuous with the barium filled terminal ileum. The filling defect caused by the lips has been variously described as resembling a spindle, a shark mouth, the beak of a lark, etc. depending upon the fanciful imagination of the authors (Fig. I to IV).

Although the commonest site of the ileo-cecal valve is on the medial aspect of the cecum, variations do exist in its location depending largely upon the cecum. If the cecum is partially rotated the ileo-cecal entrance may be found on the lateral border or even towards the posterolateral margin of the cecum, making it extremely difficult to see in a single antero-posterior projection when filled with barium. A mobile cecum may cause a great variation in position of the ileo-cecal valve from time to time depending upon the degree of fullness of the cecum and the position of the patient.

In cases where there seems to be direct implantation of the ileum into the posterior wall of the cecum, the roentgenological appearance of the ileo-cecal valve assumes a different shape from that described. There will be an ovoid filling defect in the center of the cecum with a thin line of barium across its horizontal axis (Fig. I to IV). This represents the lumen of the termi-

nal ileum visualized en face. Sometimes a stellate appearance of the mucosa is seen. In such cases a slight rotation of the patient brings it into a semi-profile view and then the appearance is exactly similar and identical to the usual medially inserted valve (Fig. VI). We believe that the insertion of ileum into the right colonic wall described by previous authors is actually a variation in the fixity of the cecum which is partially rotated, thus giving a false impression that the ileum is on the right side of the cecum (Fig. VII). At times the implantation of the ileum may be higher than usual, but under any circumstances the typical appearance of the ileocecal valve and the emergence of the terminal ileum would give a clue as to the correct diagnosis. For example, Fig. IX presents a case which was clinically diagnosed as carcinoma of the cecum and the barium enema study revealed a pseudo-filling defect. Surgical exploration against radiological advice revealed it to be just a high implantation of the ileum with normal ileocecal valve.

Variations in the size and shape of the lips are protean. The upper lip, which is usually longer than the lower one, may be of equal length or even shorter. Some lips are thinner and longer; some are short and plump with variations between the two extremes. An enthusiastic attempt at a correlation of the size and contour of the ileocecal valve to the usually described hypersthenic, sthenic and asthenic habits of the individuals resulted in utter disappointment and discouragement.

The thickness of the lips also vary from person to





Fig. 9. High insertion of the ileocecal valve: (a) barium enema; (b) post evacuation exposure. The surgeon operated against radiological advice and the high insertion was corroborated. No lesion was present.

person and from examination to examination. When the tonus of the valve is in its maximum it gives an appearance of plumpness but when it is in a state of

relaxation it assumes its normal size. A post evacuation film in barium enema examination frequently accentuates the appearance of the ileo-cecal valve. On careful scrutiny and by critical measurements we found out the average thickness of each lip ranges between 3 and 5 mm. Anything above 6 mm. should be considered as a hypertrophied lip on a completely filled colon examination. However, strict adherence to the rigid measurements without paying any attention to other pertinent factors leads to ridiculous blunders.

#### SUMMARY

An attempt at the study of the roentgenological appearance of the normal ileocecal valve is made with a description of the technique of examination.

Correlated specimen roentgenographic study is presented supporting the observations found in the living.

The various morphological variations and the corresponding roentgenological appearances are described.

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Fig. 10. Sphincteric action at the ileo-cecal valve.

## EFFECTIVE MEDICAL MANAGEMENT OF PEPTIC ULCER AND GASTRITIS

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**D**ESPITE THE immense amount of investigation into the causation of peptic ulcer, the specific etiology of the condition remains obscure. There is, as yet, no definite etiological factor and no specific therapy based on pathogenesis of the lesion. Review of the literature indicates that the most prevalent of the theories on the development of ulcer center around excessive production of free hydrochloric acid, hypermotility and decreased duodenal tissue resistance. Hypersecretion of gastric juice is almost always associated with duodenal ulcer, while loss of tissue resistance seems more characteristic of gastric ulcer (1). Unfortunately, the exact nature of the abnormalities preceding breakdown of the mucosal resistance to acid and pepsin also remains unknown. Possible roles of mucin deficiency, excessive lysozyme activity, vascular disturbances, hepatic disease, intrinsic cellular abnormalities and endocrine disturbances have in vain been considered (2). Therefore, since etiologic investigations have only served to confirm the concept, "no acid, no ulcer" (2), the medical treatment of peptic ulcer must be directed at reduction of acidity and motility, thereby affording some degree of protection to the ulcer crater and the irritated mucous membrane.

The parietal cell, the source of hydrochloric acid, is extremely susceptible to stimulation by emotional excitation. Investigation has shown that gastric secretion in man is predominantly under neural control (3). Therefore, the theory that peptic ulcer is a psychosomatic disease has gained recognition in recent years. That psychologic factors are involved in ulcer formation cannot be denied. (3).

The need for employing an understanding and sympathetic attitude and for providing liberal amounts of reassurance should be recognized by every physician as an integral part of the medical therapy of peptic ulcer. Psychoanalysis alone adds little.

Our aims in the treatment of peptic ulcer should be to reduce gastric hyperacidity and hypermotility, to aid the patient in understanding and handling his environmental and emotional problems, and to improve his general health. The patient should realize early that while he may be symptom-free, it will require at least three to six months to heal a simple peptic ulcer. Inadequate handling of patients and insufficient periods of treatment after the first attack, account for most of the failures and recurrences experienced in peptic ulcer cases.

The control of hyperacidity and hypermotility is approached by diet, sedation, antispasmodics and last, but not least, by antacids. These will now be discussed.

**Diet.** Proper diet is an important adjunct to medical management of peptic ulcer. The principle involved is

the frequent feeding of bland foods providing adequate proteins, carbohydrates, calories, minerals and vitamins. These foods provide at the same time some acid-buffering capacity. A careful dietary regimen protects the stomach and duodenum from chemical, mechanical, and thermal irritation, which would increase acid production and motility (4).

**Sedation.** Sedation is important. It should be induced by long-acting drugs which do not depress or confuse the individual patient. The new tranquilizers may supplant the older type of sedation.

**Anticholinergics.** Unfortunately, "medical vagotomy" through the use of anticholinergic drugs has not by itself proved adequate. Methantheline bromide, diphenmethanil methylsulfate, and other drugs which block stimulation of the vagus nerve will reduce hyperacidity, but have relatively little effect on cephalic secretory rate. Anticholinergics, in adequate doses, exert untoward systemic effects. This inhibits their widespread use. The use of these compounds alone in the treatment of peptic ulcer is not recommended, but they do have definite value as adjuncts to antacid and sedative medication.

**Ganglion-blocking agents.** Compounds such as tetraethylammonium bromide and hexamethonium bromide are effective in lowering gastric acidity and motility. However, often accompanying their action on gastric function is a sudden fall in the blood pressure (5). This has led to their use being largely abandoned in the treatment of gastric disorders.

In recent years, many substances have been advanced as ulcer "cures." Among these can be listed: gastric mucins which have been shown to lose their mucosa-coating qualities even in a moderately acid medium (11); anion-exchange resins which in practice enjoyed the stage for a short period (5); the hormones from intestinal mucosa, enterogastrone and urogastrone, which have been shown to be ineffective in man (7); combinations of drugs which have given unspectacular results (3); and extracts of various endocrine glands which are so far valueless (8).

Through a method of *in vitro* appraisal of antacid capacity (6) it has been demonstrated that even certain widely used antacids have much lower antacid capacity in pepsin-hydrochloric acid solution than in a solution of the acid alone.

The importance of antacids in ulcer therapy cannot be overemphasized. Because of this, we have seen continued efforts to improve existing antacids. Sippy powders have a high capacity to neutralize acid, but contain absorbable alkaline ions which commonly lead to varying degrees of alkalosis when taken in adequate doses. Calcium carbonate has the advantages of high

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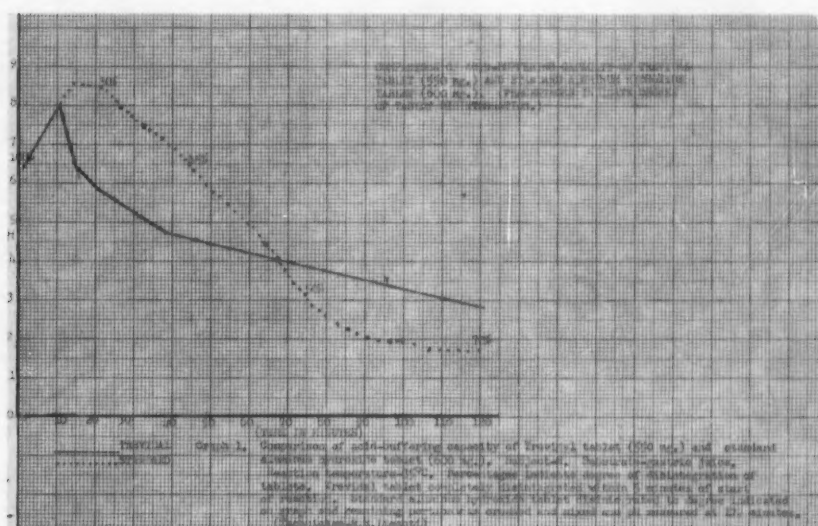


Fig. 1

TREVIDAL

STANDARD

Graph 1. Comparison of acid-buffering capacity of Trevidal tablet (550 mg.) and standard aluminum hydroxide tablet (600 mg.). Subject—R. Substrate-gastric juice. Reaction temperature—35°C. Percentages indicate degree of disintegration of tablets. Trevidal tablet completely disintegrated within 5 minutes of start of reaction. Standard aluminum hydroxide tablet disintegrated to degree indicated on graph and remaining portion was crushed and mixed and pH measured at 122 minutes. (Technician—R. E. Liechti).

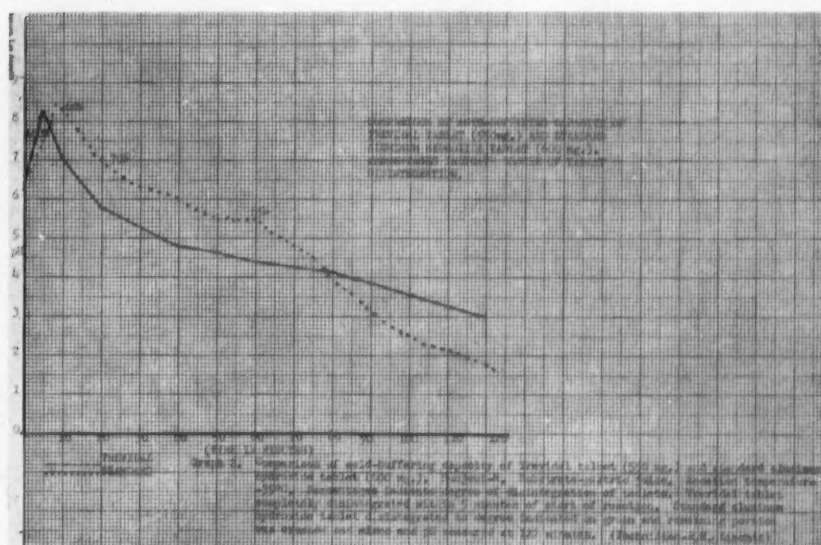


Fig. 2

TREVIDAL

STANDARD

Graph 2. Comparison of acid-buffering capacity of Trevidal tablet (550 mg.) and standard aluminum hydroxide tablet (600 mg.). Subject—M. Substrate-gastric juice. Reaction temperature—35°C. Percentages indicate degree of disintegration of tablets. Trevidal tablets completely disintegrated within 5 minutes of start of reaction. Standard aluminum hydroxide tablet disintegrated to degree indicated on graph and remaining portion was crushed and mixed and pH measured at 122 minutes. (Technician—R. E. Liechti).



antacid capacity and rapid onset of action, but it tends to cause constipation and has a brief duration of effect.

Also well known is the slow mild antacid action of aluminum hydroxide, but it has the additional drawbacks of constipation and tendency to produce concretions. Magnesium trisilicate, though non-constipating and having no systemic effects in ordinary doses, has a slow onset of action and brief acid-buffering activity.

Further research then brought forth combinations of antacids, providing a higher degree of efficacy with the undesirable effects of one ingredient offset by opposing tendencies of another ingredient. Magnesium carbonate was noted to control the constipating effect of calcium carbonate, and therefore these two have been combined (1). Still, this combination has brief action, is unpalatable, and does not form a protective colloid film on the gastric mucosa (9).

Similarly, magnesium trisilicate has been used in combination with aluminum hydroxide, to counteract the strong tendency of the latter to cause constipation. However, the net result of this combination has been low antacid capacity, slow neutralization of acid, and an unpalatable product. These "old" combinations have become, by far, the most widely employed and have sustained their dominant positions in spite of their known drawbacks.

A new antacid, Trevidal®, has incorporated four

\*Trevidal® produced by Organon Inc., Orange, New Jersey.

proven clinically effective antacids—calcium carbonate, magnesium carbonate, aluminum hydroxide, and magnesium trisilicate—in carefully determined proportions which provide maximal therapeutic effectiveness, yet avoid tendencies to produce either constipation or diarrhea, to upset the systemic acid-base balance, to induce "acid-rebound," or to interfere with absorption of nutrient factors (10). This antacid also contains a *hydrophilic colloid*† with good viscosity, adhesiveness, and spreading qualities even in highly acid gastric juice (11), thus affording protection to the gastric mucosa. Trevidal also has a binding material which comes from cooked oatmeal\*\* and serves to release the antacid charges steadily for prolonged acid-buffering activity. Favorable reports by others (2,9,10) induced the author to perform *in vitro* and *in vivo* studies with this newly developed antacid.

*In vitro studies.* Ten different gastric aspirations†† comparing the solubility and acid-neutralizing effects of this new antacid (Trevidal) and a standard aluminum hydroxide preparation were made. Immersed in 10cc samples of fresh gastric juice from four duodenal ulcer patients at a reaction temperature of 35°C, the Trevidal tablet began to disintegrate almost immediately, and within five minutes had completely disinte-

† Regonol®—cyanopsis tetragonoloba gum.

\*\*Egraine®.

†† Conducted by Mr. R. E. Liechti.

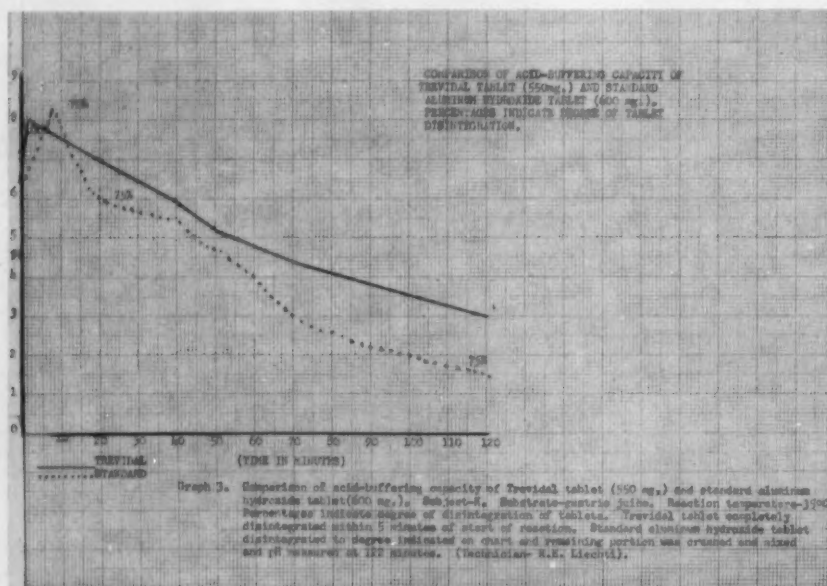


Fig. 3

— TREVIDAL  
..... STANDARD

Graph 3. Comparison of acid-buffering capacity of Trevidal tablets (550 mg.) and standard aluminum hydroxide tablet (600 mg.). Subject—K. Substrate—gastric juice. Reaction temperature—35°C. Percentages indicate degree of disintegration of tablets. Trevidal tablet completely disintegrated within 5 minutes of start of reaction. Standard aluminum hydroxide tablet disintegrated to degree indicated on graph and remaining portion was crushed and mixed and pH measured at 122 minutes. (Technician—R. E. Liechti).



grated. The standard tablet had not disintegrated after more than one hour and had to be crushed and mixed with the gastric juice before obtaining final measurement of pH. (See graphs 1, 2, 3, 4). It should be mentioned here that early Trevidal tablets which were tested under the same conditions, proved to be no better than the standard, but later tablets which were made available for this study were found to disintegrate in the time reported above.

**Gastroscopic Examinations.** Gastroscopic examinations were performed on eighteen patients forty-five minutes after the ingestion of two Trevidal tablets. The tablets were shown to have disintegrated and spread fairly evenly over the gastric mucosa.

**Clinical Study.** Using this new antacid, a study was made of its effect on sixty-nine patients complaining of severe epigastric symptoms. Ages ranged from 26 to 81 years, with the greatest frequency being in the fourth, fifth and sixth decades. Differential diagnosis was made from clinical, X-ray and gastroscopic examinations, and the conditions were categorized as follows: Simple duodenal ulcer, 45; ruptured ulcer, 2 (treatment in these patients began after surgery); hemorrhagic duodenal ulcer, 6; gastric ulcer, 3; stomal ulcer, 3; gastritis, 6; functional dyspepsia, 4. All patients were put on a regimen consisting of two Trevidal tablets every 2 or 4 hours and whenever symptoms of distress occurred, and were instructed to adhere to a bland diet. In the more severe cases antispasmodics and sedation were added to the regimen.

## RESULTS

Of the forty-five patients with simple duodenal ulcer, 35 (80%) became symptom-free. Partial relief of symptoms was obtained by eight patients (18%). Because of emotional disturbances in these latter patients, an antispasmodic and sedatives were added to the antacid regimen, and then good relief of symptoms was obtained. One of the two patients in this group who reported no relief was later hospitalized and underwent surgery for a penetrating ulcer. A second patient claimed no relief, and another complained of more distress with flatulence and belching soon after the taking of the tablet. One patient was constipated with both Trevidal and the aluminum hydroxide preparation. Another patient complained of the tablets sticking in his teeth when he chewed them.

In the six patients with gastric and stomal ulcers, favorable results were obtained in five (83%), with no detectable improvement in one. Results in patients with hemorrhagic duodenal ulcer were equally impressive. Noticeable improvement was observed in all of these patients with especially good results in five (83%).

In the six patients with gastritis (as diagnosed by gastroscopic studies) four (66%) obtained good results and complete relief of symptoms, while two reported incomplete or no relief.

In the four dyspeptic patients, two reported complete relief of their symptoms. The two remaining patients

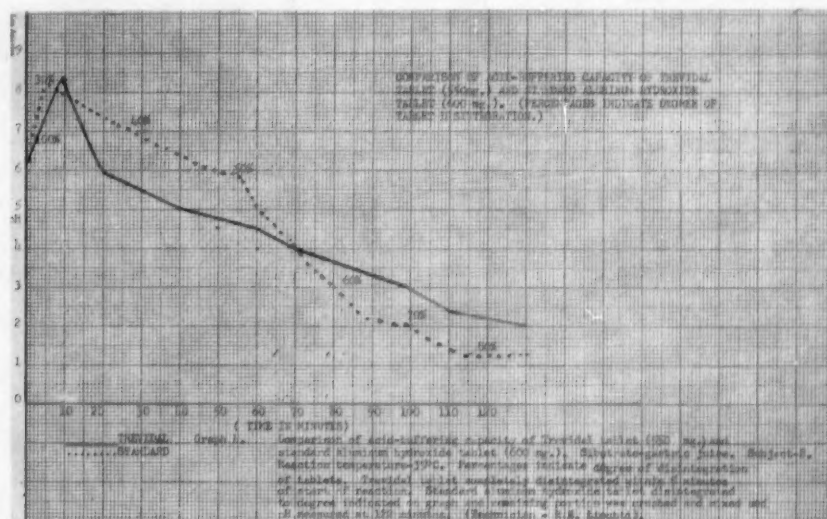


Fig. 4

— TREVIDAL  
- - - STANDARD

Graph 4. Comparison of acid-buffering capacity of Trevidal tablet (550 mg.) and standard aluminum hydroxide tablet (600 mg.). Substrate—gastric juice. Subject—B. Reaction temperature—35°C. Percentages indicate degree of disintegration of tablets. Trevidal tablet completely disintegrated within 5 minutes of start of reaction. Standard aluminum hydroxide tablet disintegrated to degree indicated on graph and remaining portion was crushed and mixed and pH measured at 122 minutes. (Technician—R. E. Liechti).

did not remain under treatment for sufficient length of time to permit evaluation of the antacid.

Since the physician is concerned with the side effects of the antacid which he prescribes, patients were instructed to report any disturbance in bowel function or other symptoms commonly encountered. As described above, complaints from patients were few.

#### SUMMARY

Despite many medical "advances" in peptic ulcer therapy, the physician must still rely on an effective antacid as an essential part of peptic ulcer therapy.

A new antacid, Trevidal®, is a balanced combination of ingredients having clinically established value as antacids, plus a demulcent gum with optimal viscosity and mucosa-coating qualities even in highly acid gastric juice.

In *in vitro* studies, this antacid exhibited more rapid disintegration and as prolonged an acid-neutralizing activity as a corresponding standard aluminum hydroxide preparation.

Gastrosopic examination of eighteen patients forty-five minutes after the ingestion of two Trevidal tablets revealed almost complete disintegration of the tablet and a coating of this antacid spread over most of the gastric mucosa.

A group of sixty-nine patients with varied conditions causing epigastric distress were studied (duodenal, gastric and stomal ulcers, gastritis, and dyspepsia of undetermined origin). These patients were typical of the ambulatory types commonly seen in general practice. The regimen consisted of Trevidal, dietary adjustment, antispasmodics and, when necessary, sedatives in those patients with emotional disturbances. Overall ex-

cellent results were obtained in most patients through use of this antacid. There were only minor reactions resulting from its use.

From the results obtained in this study, it appears that this new antacid is a valuable contribution to the effective medical management of peptic ulcer and gastritis. In practice, all methods of control of peptic ulcer should be used concurrently.

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## THE GLUCOSE HOMEOSTASIS TEST

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GLUCOSE tolerance tests for the diagnosis and evaluation of diabetes mellitus have been in use for almost fifty years. The term, "tolerance," suggests an estimation of the body's ability to tolerate some amount of glucose before the mechanism that metabolizes that substance exceeds its capacity. In 1924, Seale Harris devised his "six hour glucose tolerance test" for the diagnosis of a newly discovered disease—functional hyperinsulinism (1). Since that time a vehement and, occasionally, acrimonious controversy has raged over the question as to whether functional hyperinsulinism actually exists (2,3). Not a little of the confusion is caused by the astonishing fact that it is actually difficult to have Harris's test done properly. It is regrettable that in too many laboratories, a request for the test is answered by determinations of the blood glucose level for as long a period as the technician feels like doing the work—usually four hours or less. Since the test is designed to show the efficiency of the apparatus that regulates the blood glucose level, it is semantically more correct to refer to it as the "glucose homeostasis test." Then there will be no confusion with the usual glucose tolerance test which, as will be demonstrated, *should be performed with a distinctly different technique*. With the removal of this confusion, the clinician will stand a better chance of getting the laboratory work done as he wishes it.

In order intelligently to apply the test, we must first establish the criteria and conditions under which it is performed and evaluated. First, there can be no question that the analyses *must* be made by some method that gives "true blood glucose." The discrepancy caused by "non-glucose reducing substances" when using the Folin-Wu technique, which has been believed to lie between 10 and 30 mgs. per 100 cc. (4), has been shown to vary between 1 and 78 mgs. per 100 cc. The differences even changed in completely irregular fashion during the course of a single glucose tolerance test and the larger discrepancies were found with high and low blood glucose levels indiscriminately (5). Now, in investigating diabetics, an error of that magnitude might not interfere seriously with the correct diagnosis although, occasionally, the presence of unusually large amounts of "saccharoid" material has led to almost tragic errors in calling normal people diabetic (6). However, in determining the lower blood glucose levels the error, percentage-wise, becomes prohibitively large.

Venous blood is preferred to arterial (finger tip) blood for the ordinary glucose tolerance test for diabetes (7). The difference in arterial blood glucose levels after the administration of glucose between normals and diabetics might not be very great. In the diabetic, due to the paucity of insulin, there is an impairment of the ability of the tissues to absorb glucose from the blood and there is therefore a diminution in the arterial-venous blood glucose difference. This makes

the venous blood glucose level diagnostic for the diabetic. Furthermore, the notion of a renal threshold for glycosuria to appear is based upon venous blood glucose levels.

On the other hand, the glucose homeostasis test requires *arterial* blood. In the fasting state, arterial and venous bloods contain sensibly the same amount of glucose. If the glucose is then administered, both arterial and venous blood glucose levels rise, the former much more than the latter, the maximum arterial blood glucose concentration being reached in about half an hour. The venous level reaches its maximum a little later. This, of course, is considerably lower than the arterial level since the tissues are absorbing glucose from the blood as it passes through them. Then both curves fall more or less parallel to each other. In about two hours, the arterial concentration reaches its initial level but the venous level may continue to fall for several minutes. By taking samples frequently enough it is usually possible to catch a level of venous blood glucose that is distinctly hypoglycemic. This has been explained as the result of accelerated absorption of glucose by the tissues which had been starved by the overnight fast (8). Then the venous level rises again as equilibrium is reestablished between the blood and tissues and, after the third or fourth hour, both curves become approximately horizontal lines, the arterial being slightly higher than the venous.

In order to decide unequivocally which blood is preferable for the glucose homeostasis test, a comparison was made between the two bloods. Six subjects were examined half an hour after the administration of 100 grams of glucose (in solution). Each was required to clench and open his right fist alternately until fatigue prevented further motion. This usually took but two minutes. Three minutes later samples were drawn from each median cubital vein and each middle finger tip by four technicians in order to secure the samples as nearly simultaneously as possible. No tourniquet was used. Digital pressure on the vein above the elbow was sufficient to secure the small amount of blood required by the micro method employed. The fasting levels were deliberately not taken in order not to puncture the veins unnecessarily.

Obviously, arterial blood should be used because it is practically constant in composition all over the body.

Patient	Right Elbow	Left Elbow	Right Finger	Left Finger
1	124	129	183	184
2	146	158	204	204
3	139	148	178	172
4	99	111	132	130
5	100	108	124	125
6	122	130	164	164

None of these subjects was diabetic.



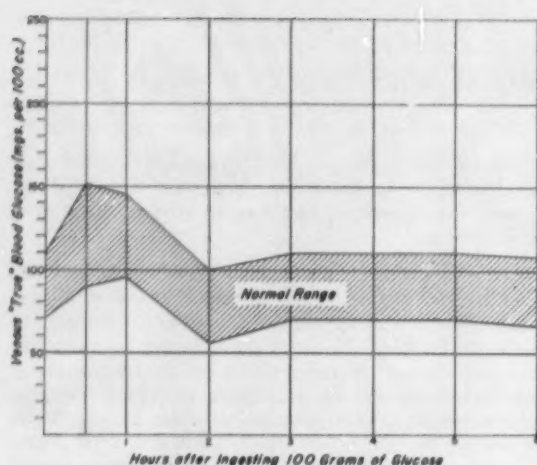


Figure 1.

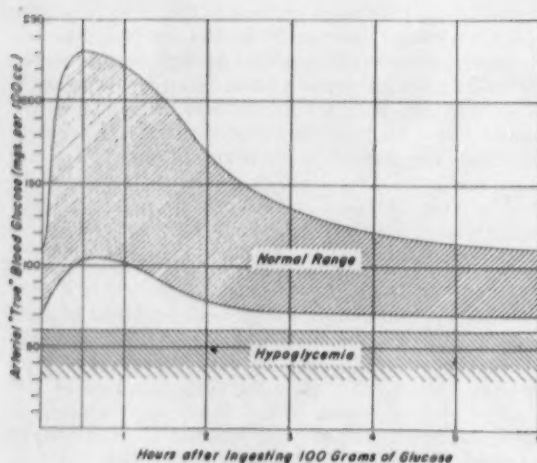


Figure 2.

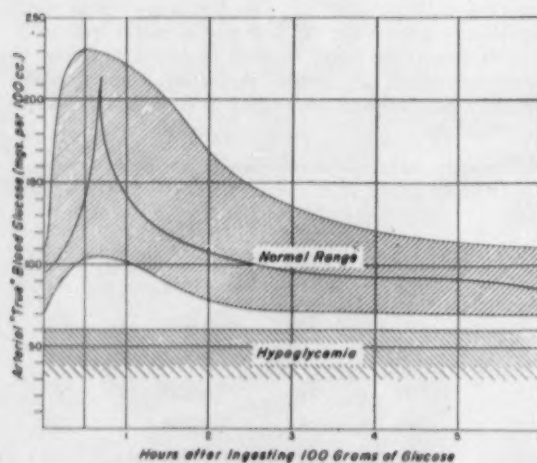


Figure 3.



Figure 4.

Venous blood drawn from the elbow really gives the amount of glucose left in the blood *after* the tissues distal to that point have taken some sugar out. Therefore, the venous blood sample contains less sugar than the arterial and the difference was greater in the right arm which had been exercised to increase glucose utilization. Furthermore, analysis of blood drawn from the elbow gives no information about the concentration of glucose in, say, the renal veins whereas we may safely assume that the renal arteries contain the same amount of glucose as those in the finger tips. Glucose is so active metabolically that we should have information applicable to the entire body rather than to a single portion which is picked out solely because of its accessibility.

In hypoglycemic states, there may be a reversal of the arterial-venous blood glucose difference, the venous blood containing *more* glucose than the arterial. Fabrykant, Ashe and Allen state, "... we are led to believe the reversal of the A. - V. G. D. recorded in our observations was produced by diffusion of glucose from tissues or tissue spaces into the circulation. We also feel that this passage of sugar into the blood stream occurred in response to the fall of arterial blood sugar and that it represented an attempt on the part of the body to correct the critically low concentration of sugar in the arterial blood." (9) Therefore, if venous blood be used for the glucose homeostasis test, two errors are possible. The early hypoglycemic phase might occur at a time when a sample is drawn and therefore lead to an erroneous diagnosis of hyperinsulinism. On the other hand, the late drop might be missed entirely.

Another reason for using arterial blood lies in the fact that we must puncture one of the cubital veins at least four times in the course of a six hour test. This procedure becomes painful and the approach of the dreaded needle to the sore arm often produces enough apprehension to raise the blood sugar by adrenal action, thereby vitiating the test. The finger prick is far less cruel and, if a deep enough wound is made for the first sample, the subsequent ones may be obtained by wiping the loose clot with some gauze.

Frequently, after hypoglycemia is reached and its symptoms are induced, subsequent blood sugar values will be somewhat higher. This is due to the outpouring of adrenal hormones in response to the abnormally low blood sugar concentration. The resultant glycogenolysis raises the blood sugar from the unsafe low value. This is the normal equilibrating mechanism. In performing the glucose homeostasis test, it is not always necessary to continue the determinations for the



full six hour period. Once the level has dropped below 60 mgs. per 100 cc., it is not necessary to wait for any further drop or a compensatory rise. The patient should be fed and the test terminated.

The usual graphic representation of the glucose tolerance test with its straight lines connecting the blood sugar values gives a false picture of what actually happens in the course of a test. The blood sugar does not decide to change its trend abruptly at exact hours after the ingestion of glucose as is shown in the chart of normal venous blood sugar curves (Fig. 1) (1).

Fasting	1	2	3	4	5	6 hours after 100 grams of glucose.
91	88	103	66	94	95	104 mgs. glucose per 100 cc. of blood.

There is, of course, a gradual change all along the course of the test. The chart (Fig. 11) does not represent any particular curves. The limits of the "normal range" were not taken from just two curves. Each point was the highest or lowest blood sugar for that particular time obtained with 100 normal subjects. Only three points on the upper limit came from one glucose homeostasis test and but two on the lower boundary from another single curve. There are so many variables

Fasting	1	2	3	4	5	6 hours after 100 grams of glucose.
71	166	118	88	75	70	53 mgs. glucose per 100 cc. of blood.

in the complex process of absorption and metabolism of the glucose that any further analysis of the curves is meaningless pedantry.

By taking samples each minute during the first hour, it was seen (in 5 cases) that the curve rises to a sharp peak and then drops to about the middle of the "normal range" in a few minutes. The peak can occur at any time between 5 and 50 minutes after the ingestion of the glucose. The height and duration of the rise have no clinical significance. Theoretically, it is important because it is this rise which stimulates the insulin apparatus to produce the insulin that enables the liver and muscles to absorb the glucose from the blood. One such experiment is included (Fig. III). Similar findings have been reported by other investigators (10,11, 12,13.), but most of the older work was done with the Folin-Wu method of analysis.

The difference in blood sugar between, say 80 and 200 mgs. per 100 cc. seems to be very large. However, this difference (120 mgs. per 100 cc.) represents an increase of but 7 grams of glucose in the entire circulating blood. There is a great difference of opinion as to the amount of glucose that should be used for the test. Most of the glucose ingested is immediately converted into fat (14) and there isn't much point in adjusting the amount of glucose to the weight of the patient. Furthermore, there are unpredictable differences in the rapidity of absorption through the gastrointestinal tract. Changing the amount of glucose administered does not appreciably affect the height of the rise but larger amounts tend to prolong it. Striking an average among the amounts proposed, it was felt that 100

grams of glucose would be satisfactory. Such has been found to be the case in over two thousand tests. 200 ml of a 50% solution, which can be prepared in bulk by dissolving powdered glucose in boiling water (in which it dissolves almost instantaneously) and making the proper dilution and then keeping in the refrigerator, are mixed with 25 ml of bottled "reconstructed lemon juice" for each test. The cold, flavored drink is well tolerated. It should not be necessary to add this word of caution, but a highly reputed laboratory reported a test as follows:

This curve seemed strangely undulating and it was discovered that the patient had been given 100 grams of glucose stirred into a glass of cold water. Obviously, the first rise was due to that portion of the glucose which had already dissolved and then the subsequent rise was due to the delayed solution of the rest of the glucose. The analyses were done on venous blood by the Folin-Wu method. The test was repeated after a few weeks and following values were obtained:

Thus, if we wish to determine the effect of a stimulation of the islands of Langerhans, we must administer the glucose in complete solution so that the proper stimulus is applied.

A diagnosis of functional hyperinsulinism is indicated by a drop below 60 mgs. per 100 cc. Normally, the arterial true blood sugar should not fall below 70. The "no man's land" between the two regions is the area where the results of the test are equivocal. This has never been encountered in over 2000 consecutive tests. A positive finding is indicated by a drop into the hypoglycemic range no matter when that state is reached. Nothing could be gained by prolonging the patient's discomfort, so the test is terminated by giving him a glass of milk—which is generally most welcome. This is much better than orange juice which is absorbed more rapidly and sometimes induces another hypoglycemic episode while the patient is on his way home.

Organic hyperinsulinism (insuloma, hypertrophy, etc.) is indicated by an initial fasting level below 50 mgs. per 100 cc. (15). In such cases, the prolonged test is superfluous.

There are rare cases of *Dysinsulinism* in which there is an initial diabetic curve followed by a dip into the hypoglycemic range. Harris postulated a time lag in the elaboration of insulin in response to a metabolic demand with a subsequent overproduction of the hormone (1). This test will not demonstrate that condition. Where this state of affairs is present, there will be an initial value above 110 mgs. per 100 cc. and/or marked glycosuria in the first two hours. Therefore, as a routine, a urine sample, taken just before

the end of the second hour, is tested for glucose. If this specimen contains glucose or the initial blood glucose was high, an additional sample of *venous* blood is drawn at the second hour. The diabetic phase of dysinsulinism is demonstrated by a concentration of glucose in this sample over 100 mgs. per 100 cc. (6).

While any method which gives true blood sugar and which can be done on a micro scale can be used, the following modification of the Folin-Wu technique has so many advantages that it should be included in this discussion. The essential feature is a stable, one solution protein precipitant that removes the non-glucose reducing substances that are largely confined to the cells. It does this by avoiding laking. No anticoagulant is required.

#### REAGENTS

**Tungstic Acid.** Dissolve 11.11 grams of sodium tungstate ( $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ ) and 5.00 grams of sodium citrate ( $\text{Na}_3\text{C}_6\text{H}_5\text{O}_7 \cdot 2\text{H}_2\text{O}$ ) in about 500 ml. of water. Dissolve 13.60 grams of fused sodium bisulfate ( $\text{NaHSO}_4$ ) or 15.60 grams of the crystals ( $\text{NaHSO}_4 \cdot \text{H}_2\text{O}$ ) in about 400 ml. of water. Mix the two solutions and dilute to 1 liter with water. Allow the mixture to stand for a week and filter. This solution keeps indefinitely. *Folin-Wu Alkaline Copper Tartrate and Phosphomolybdic Acid Solutions.*

**Benzene ( $\text{C}_6\text{H}_6$ ).**

**Standard Glucose Solution.** A solution of purest glucose in saturated benzoic acid containing 0.100 mg. glucose per ml.

#### APPARATUS

*Boiling water bath, 2 or 3 ml centrifuge tubes, 0.1 and 0.5 ml. pipettes calibrated "to deliver," reservoir microburette graduated to 0.01 ml. (The Machlett Automatic Burette is ideal for this purpose), test tubes graduated at 5.0 and 10.0 ml. (Klett cuvettes are suitable) available colorimeter or photometer that can be adapted for micro determinations, wax cups, blood lancet, cotton.*

The wax cups (16) are easily prepared by pouring melted paraffin wax into a small muffin tin whose depressions have been moistened with a liquid detergent. On cooling, the outer portions of the wax solidify first. Then, as shrinkage takes place, the upper surface of the wax forms a smooth depression that permits collection of the sample. Fig. IV. The blood will remain fluid on the smooth surface long enough to catch the sample from the finger and to pick it up into the pipette.

#### PROCEDURE

1) Allow 0.90 ml. of tungstic acid to run out of the burette into a small centrifuge tube.

2) Dip the end of the middle finger into some alcohol and make a lancet wound. Dry the finger tip with cotton. With *gentle* pressure above the distal point, express a few drops of blood, catching them on the depressed surface of the wax cup where they will flow to-

gether in the center. Instead of holding the finger palmar side up, it is more convenient to have the hand turned palm down. By placing the wax cup on a small mirror, one can watch the blood ooze out of the wound and, when enough has collected, it can be caught on the cup by drawing the finger over the fairly sharp edge.

3) Pipette 0.10 ml. of the blood into the tungstic acid in the centrifuge tube. Stopper the tube with the index finger and support the tip with the thumb. Shake the tube vigorously along its length a few times to secure homogeneity.

4) Allow the tube to stand just long enough for the pink color of the coagulum to *begin* to turn brown. It should not stand long enough to turn dark brown. Centrifuge rapidly for a minute.

5) Introduce the tip of a 0.50 ml. pipette into the clear fluid, taking care not to disturb the sediment, and draw the clear fluid up to the mark.

6) Transfer this fluid into a graduated test tube. Add 0.50 ml. of alkaline copper tartrate and a drop of benzene. Plug the tube with a bit of cotton. Shake momentarily.

7) Place the tube in boiling water for 6 minutes. Remove the tube from the water bath and place it in a rack. Immediately add 0.50 ml. of phosphomolybdic acid and shake gently for a few seconds to expel the  $\text{CO}_2$ . Add water to the 5.0 mark (or to the 10.0 graduation for higher sugars) and mix by inversion, stoppering the tube with the finger.

8) Compare with the standard which has been prepared by placing 0.50 ml. of the standard glucose solution in a graduated test tube and treating it according to steps 5 to 7. The standard corresponds to a blood sugar of 100 mg. per 100 cc.

That this method gives "true sugar" was established by comparing it with yeast fermentation, the macro Folin-Wu and Lauber and Mattice methods. For this investigation, venous blood was used because of the sample required. Each sample was drawn into a dry sterile 5 ml. syringe fitted with a 1 inch 20 gauge needle, 5.5 ml. being taken in each case. 0.5 ml. was discharged onto the surface of a wax cup; the rest was placed in an oxalated tube. From the portion on the cup, three 0.1 ml. portions were taken. One was analyzed according to the method of Lauber and Mattice (17). (A). The second was treated by the above method (B). The third was treated similarly but the mixture of blood and tungstic acid was allowed to stand for an hour before centrifuging (C).

The oxalated sample was analyzed for "true sugar" by the double procedure, using yeast fermentation, given by Peters and Van Slyke (18). This gives the Folin-Wu sugar (19) (D) and the "non-glucose reducing substance" (E). Their difference (D - E) is the "true sugar."

The results of these determinations are given in tabular form—

Sample → Method ↓	1	2	3	4	5	6	7	8	9	10
A	82	92	159	116	99	229	71	104	115	169
B	81	92	159	118	98	222	68	99	117	171
C	96	118	185	130	132	252	80	126	129	184
D	96	117	188	146	136	265	81	130	130	184
E	16	25	32	26	36	40	12	29	15	20
D - E	80	92	156	120	100	225	69	101	115	164

Comparing A, B, and D - E, we see that this method gives results sensibly the same as Lauber and Mattice's and the yeast fermentation methods. From C and D, we notice that the "non-glucose reducing substances" tend to redissolve in the filtrate on standing for an hour so that the sample must be centrifuged without delay. While the Lauber and Mattice technique (and other zinc precipitation methods) are just as accurate, this method has the very great advantage of requiring but a single precipitating reagent to remove the non-glucose reducing substances together with the proteins. This eliminates sources of error by reducing the number of volumetric measurements. The reagent is very easy to prepare. Even a fairly rough balance is more accurate than the most precisely calibrated volumetric glassware and we do not have to prepare any solution like the  $\frac{2}{3}$  N sulfuric acid of Folin and Wu by volumetric estimation. Furthermore, there is no need to balance two solutions by mutual titration as in the zinc methods. This method has the further advantage of rapidity, a determination taking less than 10 minutes so that a patient who has already reached an hypoglycemic level may be relieved of his discomfort as soon as a conclusive figure is obtained.

## SUMMARY

The diagnosis of functional hyperinsulinism would be made more frequently if the test for that condition were made more reliable and less confusing. It is proposed that the test be called "the glucose homeostasis test" rather than the currently used expression, "six hour glucose tolerance test" because the former term is actually what is determined. This will avoid confusion with the glucose tolerance test for diabetes which is done for a shorter period and which should be done with an entirely different technique. Diabetes is best demonstrated in venous blood; hyperinsulinism in arterial. The method of analysis in either case should give true blood sugar. A modification of the Folin-Wu method which has the advantages of rapidity, accuracy and ease of manipulation is suggested although any standard procedure for true blood glucose may be used.

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## EFFECT OF YOGURT WITH PRUNE WHIP ON CONSTIPATION

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CONSTIPATION is a disturbing symptom in our present mode of living, with its tension, stress and constant verbal barrage, via radio and television, for the cure of the "laxative habit." It is a challenging problem in treating the elderly and chronically ill.

Since Biblical times, Yogurt has been used as a food and to eradicate intestinal putrefaction and auto-intoxication. It is a natural physiological product of pasteurized milk inoculated with selected laboratory controlled strains of *Lactobacillus bulgaricus* and *Streptococcus thermophilus*. Its action is to remove the putrefactive and other organisms which normally inhabit the intestinal tract by changing the flora. Yogurt has essentially the same effect as acidophilus milk, except (1) it is stable for a longer period of time—two weeks as compared with two days; (2) it has a uniform custardlike creamy consistency and pleasant taste, whereas acidophilus may have a sour milk taste with lumps of curd.

The use of *Lactobacillus acidophilus* for the treatment of constipation has been described by Rettger and Cheplin (1), James (2), and Kopeloff (3).

Prunes have been reported in the French literature as early as 1345, as a natural intestinal stimulant in promoting intestinal elimination without purgation.

Since it is possible to add fruit juices to Yogurt, without affecting its bacterial flora and its physiological effect, it seemed logical to add Prunes in the form of Prune Whip and study the effect on bowel habits.\*\*

The resulting Prune Whip Yogurt contained 5.5 oz. Plain Yogurt, 2.5 oz. of Prune Whip (total 8 oz.), and had the following values:

YOGURT: 5.5 oz. : 165 Gm.

Protein (2.87%) 4.74 Gm. CHo (4.9%) 8.08 Gm. Fat (3.4%) 5.61 Gm.

PRUNE WHIP:

Protein (2.27%) 1.7 Gm. CHo (45.3%) 34.08 Gm.

6.44 Gm.

42.16 Gm.

5.61 Gm.

or approximately 246.7 calories

### METHOD

One hundred ninety-four (194) patients suffering from constipation and occupying two complete hospital wards, representing a typical cross section of common chronic geriatric illnesses, were selected for the use of Prune Whip Yogurt and only the gravely ill (four cases) were not included in this study. Of these ninety-eight (98) were female with an average of 71.6 years; the youngest fifty-three (53) and the oldest ninety-one (91) years of age. Ninety-six (96) were

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\*\*Supplied as Prune Whip Yogurt by Dannon Milk Products, Inc., New York, New York.

males, with an average age of 71.6 years, the youngest fifty-four (54) and the oldest eighty-seven (87) years of age. Of the one hundred ninety-four (194), ninety-one (91) or 46.9% were diabetics; forty-one (41) males and fifty (50) females.

All the patients were destitute, chronically ill individuals and, with few exceptions, had a history of unbalanced, nutritionally deficient diets. They represented many nationalities with various food preferences and taste.

All laxative orders were discontinued on September 30, 1954, and the Prune Whip Yogurt was given as a night feeding until November 20, 1954. The basic diabetic diet was not changed.

### RESULTS

*Taste.* The Prune Whip Yogurt was accepted more readily by the females (all but three or 2.9%), than by the males (all but sixteen or 16.6%). The refusal was absolute and all persuasive efforts for further trial were futile. Of the diabetics three (3) females or 6% and six (6) males or 14.6% would not use the mixture. For the first three or four days most of the patients ate all but 2-3 oz., but within a week at least fifty percent (50%) requested a second helping. Another batch of Prune Whip Yogurt with sugar added, was prepared for the patients who had refused the original formula because of its "tart" taste. This mixture was not accepted any more readily than the first and was discontinued.

*Constipation.* Of the hundred sixty-five patients (165) who received the supplementary feeding, laxa-

tives had to be resumed in three (3) females and four (4) male cases or 4.2%. The first three or four days were very trying because, characteristic of this age group, these subjects were bowel and laxative conscious. Approximately twenty percent (20%) were emotionally unstable and presented various degrees of senile mental aberrations, varying from neurosis to psychoneurosis. Once the Prune Whip Yogurt was accepted and relished there was no further difficulty. The stools were at first hard and had a putrefactive odor that permeated the wards and was immediately noticeable to any visitor. This problem resolved itself within a week. Considerable flatus was noted in this same period. In the second week the stools tended to be frothy. Thereafter, they became soft, well-formed and no longer malodorous. Three (3) females had had



considerable difficulty with hemorrhoids, requiring local anaesthetic ointments and suppositories. These were not necessary after use of the mixture for two (2) weeks. Five (5) females and four (4) males (5.4%) had various degrees of rectal pruritus. This symptom cleared within (3) weeks. One male, E. M. age 74, had a severe rectal pruritus, following Aureomycin therapy for thrombophlebitis. After one (1) week the rectal mucosa and surrounding skin were completely clear.

A. S. age 70, had distention, quasi-paralytic, atonic ileus with poor skin and muscle tone. Her diabetes was always under good control. Laxatives were of no avail and Prostigmine and enemas were necessary. With the institution of the Prune Whip Yogurt, Prostigmine was discontinued in three (3) weeks and enemas were no longer necessary after five (5) weeks.

To date (three months later), twenty-nine (29) females (30.5%) and twenty-six (26) males (37%) have returned to their original laxative dosages. It is noteworthy that invariably there is a request for the return of Prune Whip Yogurt to relieve constipation and intestinal distress.

#### DIABETES\*

Probably because of the addition of 246.7 calories to the regular individual diabetic diet, the sugar rose in eleven (11) or 26.8% of the males and nine (9) or 18% of the females. However, the urinary sugar did not increase in proportion to the elevation in blood sugar. Six (6) males or 14.6% and four (4) females (8%) showed a slight increase in urinary sugar. In the remaining 78% of the patients, the urinary glucose virtually disappeared and the blood sugar decreased.

By the way of control, the following mixture was substituted for the Prune Whip Yogurt nightly for a period of five (5) weeks.

Food	Amount	Protein	Fat	Cho	Calories	U.L.
Prunes (baby puree)	30 Gm.	.33 Gm.	.06 Gm.	7.62 Gm.	32.34	
Whole Milk	4 oz.	4.1	4.5	6	80.9	
Dried Skim Milk	1 tbap.	2.7	0.1	3.9	27.3	
TOTAL	5 oz.	7.13 Gm.	4.66 Gm.	17.25 Gm.	140.5	

In spite of the fact that this supplementary night feeding contained 106.2 less calories than the Prune Whip Yogurt, twenty-six (26) females (52%) and twelve (12) of the males (29.2%) or 47.5% of the diabetic patients developed an increase in blood sugar. This is not an exact study and requires a more scientific evaluation at a later date but the tendency was so noticeable and significant that it seemed worthy of mention. This may be due to the fact that Yogurt aids the metabolism of carbohydrates and production of glycogens in the liver (4).

In both the diabetics and the non-diabetics, the patients were more satiated, the diet problem of extra feedings simplified and cheating among diabetics was

\*Acknowledgment: We wish to express appreciation to Dr. Thomas H. McGavack for his suggestions in connection with the diabetic part of the work.

minimal. The morale of all the patients, especially the diabetics was notably higher.

The general skin tone in the diabetics was considerably improved and the dryness of the skin in those with peripheral vascular disease—both diabetic and non-diabetic—was lessened. E. C., a seventy-six year old diabetic woman, had a "seborrheic dermatitis" with generalized poplar rash and a distressing pruritus of three years' duration, that had resisted all forms of topical, parenteral, and oral therapy. Three weeks after taking the Prune Whip Yogurt, the rash completely disappeared. Four weeks after discontinuing the Yogurt, the rash returned.

P.B., an 84 year old woman, had a varicose ulcer of the lower right leg that had not healed for ten years, in spite of good diabetic control and three operations. Within five weeks, the ulcer was completely healed and the patient was able to walk with the aid of a cane. Three weeks after the Prune Whip Yogurt was discontinued, the ulcer recurred and at present has exactly the same appearance as before the study.

#### SUMMARY

1. A mixture of Prune Whip and Plain Yogurt has been prepared and administered to one hundred ninety-four (194) institutionalized, chronically ill patients with an average age of 71.6%. Of these ninety-one (91) or 46.9% were diabetic.
2. Twenty-nine (29) or 14.5% refused to take the mixture.
3. One hundred eighty-seven (187) patients, or 95.8%, required no laxatives during the period of administration of the Prune Whip Yogurt. Of those who ate the mixture, seven (7) or 4.2% had to resort to laxatives.
4. Twenty (20) or 22% of the diabetics revealed an increase in blood sugar but little or no glycosuria.

5. Improvement in skin tone, seborrheic dermatitis, chronic ileus and diabetic ulcers was noted.
6. During the period of Yogurt administration, nursing care was simplified because of an improvement in morale. There were fewer requests for additional food.

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## EDITORIALS

## POLIO

This brief communication calls attention to the fact that Polio Virus resides in the entire digestive tract. Years ago Simon Flexner called attention to this. In the May 1955 issue of *New York Medicine*, vol. XI, No. 9, pp. 325-347, we read a Conference on "Home Treatment of Poliomyelitis," in which a case, recovering, developed parotitis (called mumps in the report). Stimson and Hodes with others participated in the discussion. May I take this opportunity to remark that rectal swabs will disclose the presence of "polio" virus? And it may be that the epityphlon (appendix vermiformis) reacts to a "polio" presence? The appendix is styled the "abdominal tonsil." Years ago Lintz, of Brooklyn reported cases (500) of the relation of tonsillitis to appendicitis.

Thomas Horace Evans, M.D., New York, N. Y.  
The New York Medical College

## OBESITY

The greatest nutritional disease in America is obesity, and not only general practitioners but also nutrition experts have a low score in attempting to treat the condition successfully. At Cornell University School of Nutrition, Ithaca, N. Y., after a three year clinic on a group of patients, only one-quarter of them achieved satisfactory weight reduction.

It is easy enough to prescribe a suitable diet for obesity, but whether or not the patient will follow it depends on the strength of his motivation and will power. In actual private practice those who obey the rules are in the minority. With women, one of the strongest motivations is pride and a desire to be able to wear smaller-sized dresses. Men can usually be impressed only by being scared for their health or their heart. The use of appetite-destroying drugs will do no good at all if the patient is defiant. Thyroid extract merely increases the appetite. Exercise has the same effect. In the case of patients with "deep" emotional difficulties, a reducing regime is a waste of time.

Actually, no one is going to enjoy wide success in reducing obese persons until the moral climate of the nation has altered. It can only alter as a result of a widespread educational campaign beginning in the schools and carried over into the daily press. The idea of abstemiousness in food is not a natural association with the *laissez-faire* of a wealthy nation and an expanding economy.

## MILD ULCERATIVE COLITIS

In a small percentage of patients with symptoms obviously arising from the colon and superficially regarded as instances of "irritable colon," the x-ray appearances of the colon, particularly the descending branch, suggest that ulcerative colitis has been present some time in the past. The loss of haustral markings

may be very obvious and sometimes, but by no means always, a history can be elicited of previous bouts of bloody diarrhea with fever. Inasmuch as these cases, when seen, are not suffering from active ulceration, we are led to the concept of abortive attacks of ulcerative colitis which heal spontaneously. Bishop (1) feels that there may be some kind of connection between mucous colitis and ulcerative colitis, since in many instances he has seen long periods of nervous diarrhea followed by true ulcerative colitis with bloody dejections and rectal ulcers, etc.

It is doubtful, however, if there is any etiological connection between the two conditions, because the bulk of reports from unbiased observers makes it clear that in the majority of cases, ulcerative colitis comes on "like a bolt from the blue," during or following a period of emotional frustration, in persons who previously had no symptoms of any kind arising from the colon, or associated with colonic dysfunction. Nevertheless, all statements regarding ulcerative colitis are open to question since the etiology has never been satisfactorily explained.

It is certain, however, that in private practice one will encounter abortive cases, or mild recurring cases in which the disease process is not extensive or actually serious or incapacitating. If we include such cases in the totals, it gives the disease a somewhat better reputation than it has received from large clinics where only the fulminating cases are seen.

- (1) Bishop, J. F.: Mild ulcerative colitis. *Am. J. Gastroenterology*, 23, 1, Jan. 1955.

## PEPTIC ULCER PROGRESSING AFTER SYMPATHECTOMY AND SPLANCHNICECTOMY FOR HYPERTENSION

Whatever the merits and demerits of splanchnicectomy for hypertension may be, it would appear, in view of increasing case reports, that before such an operation is undertaken, each patient should have a barium x-ray study of the stomach and duodenum. As everyone is aware, peptic ulcer may be present without sufficient symptoms to make its presence suspected, and this applies to patients in general. When such a patient harboring an unsuspected peptic ulcer is subjected to splanchnicectomy for hypertension, it is now clear that the operation may permit the ulcer to progress to obstruction, perforation or hemorrhage. Unfortunately the afferent fibres from the peptic ulcer zone are severed by bilateral splanchnicectomy with the result that even perforation may be symptomless until peritonitis supervenes. The afferent fibres from the peritoneum do not travel with sympathetics.

In addition to an assessment of the cardiovascular-renal system, it would appear highly advisable before performing splanchnicectomy to do a careful x-ray examination of the upper gastro-intestinal tract so that, if an ulcer is present, it may be kept in mind and its progression, which is probable, may be awaited in anticipation of serious complications.

## BOOK REVIEWS

CASIMIR FUNK. Benjamin Harrow. Dodd, Mead & Co., New York. 1955. \$4.00.

Harrow has written a fascinating book about Funk, the man who coined the word "vitamine," later changed to "vitamin." His father was a Polish dermatologist. He worked in many medical centers in Europe and for a time was associated with Abderhalden. Shortly after World War I he came to America. In 1936 he joined the U. S. Vitamin Corporation as research consultant, a position which he still holds. At 71, Casimir Funk is at the height of his intellectual vigor. His isolation of thiamine was possibly his greatest achievement. He foresaw the value of combined mineral and vitamin supplementation, as embodied in Vi-syneral, made by the U. S. Vitamin Corporation. Funk's medical interests have spread out beyond vitamins, and one of his chief studies at present has to do with some phases of cancer. The fact that the man who gave vitamins their name is still alive and active causes one to realize how much

progress has been made in medicine within the past 30 or 40 years.

THE STRATEGICAL AND TACTICAL APPROACH TO THE SURGERY OF THE ACUTE ABDOMEN. Charles Clavel. Masson et Cie, 120 Blvd. Saint-Germain, Paris 6. 3800 francs.

The present monograph is based on 22 years' experience, during which time more than 6,000 acute abdominal emergencies were dealt with. Matters of surgical technique are left for others to describe, for the author is chiefly interested in clinical diagnosis, prognosis and, above all, the decision as to whether to operate or use conservative treatment. Consequently the volume is of primary importance to general practitioners, especially those in rural areas where it is difficult to obtain the services of a consultant. The various and serious complications of abdominal surgery receive adequate attention. All phases of abdominal surgery are included.

## GENERAL ABSTRACTS OF CURRENT LITERATURE

BRICK, I. B. AND PALMER, E. D.: *Comparison of esophagoscopy and roentgenological diagnosis of varices in cirrhosis of the liver.* Am. J. Roentgen., Rad. Ther. and Nuc. Med., 75, 3, March 1955, 387.

A study of 172 cases of proved cirrhosis of the liver is presented. Relative diagnostic merit of esophagoscopy and roentgen diagnosis of esophageal varices is compared. In this series, varices were present in 62.7 percent of the cases by esophagoscopy and in 14 percent of cases by x-ray.

REYNELL, P. C.: *Therapy in experimental hepatic failure.* Brit. Med. J., Feb. 19, 1955, 459.

Acute hepatic failure was produced in rats by the injection of small quantities of carbon tetrachloride into the mesenteric vein. Vitamin supplements, large doses of liver extract, sodium glutamate, and cortisone all failed to reduce mortality in this type of experimental hepatic failure.

GROSS, J. M.: *Preparation for sigmoidoscopy in a cancer detection center.* J. International Col. Surg., 23, 1, Jan. 1955, 34.

The rectum and sigmoid colon can be rapidly cleansed and relaxed for sigmoidoscopic study in a cancer detection center by rectal installation of a solution of sodium phosphate and biphosphate. The prompt action of such a solution is a decided advantage when rapid evacuation without spasm is desired, as in cases of fecal impaction or bedside consultation. (The solution used was the Fleet Enema Disposable Unit made by C. B. Fleet Co., Lynchburg, Va.).

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BRINDLEY, G. V.: *Diseases of the esophagus: surgical treatment.* Texas State J. Med., 51, 2, Feb. 1955, 57.

Brindley reviews advances in the surgical treatment of esophageal lesions. He classifies diverticula under pulsion and traction types, the latter seldom needing surgery. The pulsion types may be removed by a one-stage diverticulectomy. Most cases of congenital tracheoesophageal fistula can be corrected by ligation and division of the fistula with primary esophageal anastomosis. Achalasia usually is treated by dilatation, but cardioplasty may be needed in some cases. When stricture is associated, resection of the lower esophagus and cardia with esophagogastrostomy may be preferable. Simple acquired strictures can usually be dilated, but sometimes the strictured area must be resected, and followed by primary esophageal anastomosis or esophagogastrostomy. Benign tumors are rare and local excision is usually sufficient. Spontaneous rupture of the esophagus or laceration should be repaired promptly. Surgery of carcinoma is more complex.

NORTH, J. P.: *Gastric ulcer.* Texas State J. Med., 51, 2, Feb. 1955, 63.

Gastric resection for gastric ulcer gives superior results to medical treatment. Resection becomes imperative when there is a reasonable suspicion of malignancy. The operative mortality in North's series was nil except in the presence of acute perforation. Where medical treatment is chosen, complete healing in 6 weeks, as demonstrated by the barium meal, should be insisted on. Otherwise, or if the patient cannot submit to serial x-ray studies, surgery becomes advisable.



HAAS, L. L. AND BAKER, B.: *Tumor outline of esophageal carcinoma*. Radiology, 64, 2, Feb. 1955, 241.

A good x-ray study of cancer of the gullet will give detailed information not only as to intraluminal involvement and the length of the lesion, but also concerning its lateral and paraesophageal extension. Such information may affect the prognosis, type of therapy and radiotherapeutic technique.

The direct tumor shadow is visible in a significant percentage of x-ray films taken with adequate technique. Even on plain films the tumor outline is frequently visible. Regression or progression of the cancer may also be followed in many cases on plain films. For a complete follow-up conventional barium studies are needed. In lesions of the cervical and highest thoracic segments, alterations of the hypopharyngeal structures (piriform sinus) and widening of the prevertebral soft-tissue shadow on lateral neck films are diagnostic. In the upper thoracic segment the tumor is outlined anteriorly by the air contrast of the trachea. Posteriorly it may be visualized by its difference in density from the surrounding structures and by superimposition upon the spine and other tissues. Tumors of the lower half of the thoracic esophagus are similarly demonstrated in density and superimposition. In the thoracic segment the lateral and right anterior oblique views are best for obtaining direct tumor shadows. A complete study should include postero-anterior, lateral, right anterior oblique and left lateral views.

HAAS, L. L. AND BAKER, B.: *Neck roentgenograms in the diagnosis of esophageal carcinoma*. Radiology, 64, 2, Feb. 1955, 234.

Cervical roentgenograms are very valuable in the diagnosis of esophageal carcinoma. Among the direct roentgen signs are deformities of the piriform sinuses and the hypopharynx and widening of the prevertebral soft tissue shadow. The prevertebral (retrotracheal) widening does not represent a direct delineation of the tumor, but is rather attributable to both the space-occupying lesion and the secondary mechanical distention. The widened space is characteristically wedge shaped, which serves to differentiate carcinoma from other lesions producing widening of the prevertebral space.

BULGRIN, J. G. AND HOLMES, F. H.: *Eventration of the diaphragm with high renal ectopia: a case report*. Radiology, 64, 2, Feb. 1955, 249.

A case of high renal ectopia with associated diaphragmatic eventration, which has only one counterpart in the literature, is presented. An analogous association of congenital diaphragmatic hernia and high renal ectopia is of occasional occurrence. The incidence of high renal ectopia in reported cases of eventration is indeterminate. Study of individual cases of eventration for associated renal ectopia is urged. Not only is this of academic interest but, should the association prove frequent, it would offer a valuable differential sign between diaphragmatic rupture and certain types of hernia on the one hand and eventration on the other.

JORUP, SIGVARD: *Colonic hyperperistalsis in neuro-labile infants*. Acta Paediatrica, vol. 41. Suppl. 85. pg. 150. Stockholm, 1952.

Jorup has made a distinction between the so-called dyspepsia in breast-fed infants and the defective adaptation accompanied by frequent, loose stools which may occur during the first weeks of life. The dyspeptic infants have frequent, loose stools which as a rule follow directly upon the meconium discharge and continue beyond three weeks of age. More than half of the infants have attacks of pain even after normalization of the stools, and Jorup considers that the majority of cases of so-called three month's colic are attributable to the syndrome described. After the disappearance of the dyspepsia the children still have a tendency to diarrhea—occurring in about 40% of those examined—and pains of the spasmus coli type. By means of roentgen examination, the author has been able to establish a distinct difference between the condition of the colon of the dyspeptic and the normal infant. In the dyspeptic cases, a resistance to the contrast enema with an often convulsively contracted colon and further a propulsive motility of the colon on feeding was found. The propulsive motility of the colon is a continuation of a peristaltic movement starting in the duodenum about  $\frac{1}{4}$  of a minute after the commencement of the feeding, reaching the cecum at about  $1\frac{1}{2}$  minutes. It is perceived as a contraction of the sigmoid colon and sometimes of the descending colon also, accompanied by an attack of pain, and terminates in defecation about 6 to 7 min. after the beginning of the feeding. This propulsive motility of the colon gives a rapid passage through the colon. Treatment with an anticholinergic drug was effective. The proper denomination for this condition is: Colonic Hyperperistalsis in Neuro-labile Children.

Franz J. Lust.

NISSEN, R.: *Diaphragmatic hernia and its surgical treatment*. Dtsch. Med. Wo. 80, 14, 467. April 8, 1955.

Para-esophageal hernias constitute an almost absolute indication for surgical intervention because of the attending risks of incarceration, bleeding and development of ulcers. In the two other types of hernia (slipped hernia, and gastric prolapse associated with "short esophagus") the clinical symptoms have to be carefully investigated to exclude the presence of other diseases. Gastric and duodenal ulcers, diseases of the biliary passages and the pancreas, and disturbances of the coronary circulation are sometimes obscured by a roentgenogram showing an impressive hiatus hernia. In the absence of complaints no treatment is required for these types of hernia. Even if it is reasonably certain that bleeding and pain are caused by the hernia, one has to remember that a reflux esophagitis due to the relaxation of the cardiac sphincter, is more likely to cause these symptoms than a doubtful incarceration. Surgical intervention has to take this into account. Not infrequently a reflux esophagitis is complicated by the formation of erosions and chronic ulcers of the esophagus; in this latter case excision plus vagotomy is the method of choice.

Franz J. Lust.

AMER. JOUR. DIG. DIS.



PICARD, R., HARDY, M. AND KERNEIS, J.: *Eosinophilic granuloma of the digestive tube*. Arch. Mal. App. Dig. Vol. 63. No. 9. Sept. 1954. p. 920.

Under the name of eosinophilic granuloma of the digestive tube two quite different disorders are described. The first, properly called eosinophilic granulomatosis is characterized by extensive eosinophilic infiltration of the stomach or of the small intestine. The second is, on the other hand, a tumoral formation, clearly delimited, this is Bolck and Vanek's *eosinophilic granuloma-blastoma*. It is this last disorder only which is studied here.

*1st case.* A man of 44 showing for three months clinical signs of cancer of the stomach with anorexia and loss of 5 kgms. *Radiological examination:* a great lacuna of the lesser curvature. *On operation:* a tumor the size of a mandarine on the posterior surface.

*Anatomopathological examination* (Prof. Agr. Kerneis). No sign of a malignant growth. Tumor formed of young histiocytes bathing in a small quantity of fundamental substance with a few fine collagenic fibers. Few vessels surrounded here and there by a ridge of lymphoid cells. But the distinguishing feature of this tumor is that it is sprinkled with myriads of eosinophilia.

No sign of allergosis. Normal eosinophilia of the blood. Radiologically normal skeleton.

*2nd case.* A man of 68. For 15 days Koenig's syndrome. *A barium enema* is blocked at the upper portion of the caecum giving an image typical of invagination by an extraordinarily transparent tumor. *Operation:* pediculated tumor of the size of a large walnut developed at the level of Meckel's diverticulum. *Further operation* 8 days later for a new invagination by a second pediculated tumor.

*Pathological anatomy* of the first tumor: same histological characteristics as those of the gastric eosinophilic granuloma. The histiocytes are more developed (fibroblasts), the fundamental substance more abundant with more collagenous fibers, more vessels, the eosinophilia numbering hundreds not thousands. Here again no allergosis, poly-eosino: 3%.

With the aid of different observations (Vanek, Bolck, Feyrter, Nunès) and our own, the distinguishing features of tumoral eosinophilic granuloblastomas may be summarized as follows.

It is a question of tumors, ranging in size from a hazel nut to a mandarine, which in 3/4 of gastric cases are situated at the level of the antrum. Sex is immaterial. The age is the same as for cancer.

At stomach level the *clinical and radiological symptoms* are those of cancer. From the endoscopic point of view there is the image of hypertrophic gastritis.

When they are intestinal they are always in the ileum and the image is that of an invagination.

*The pathological anatomy* is simple: it is a granuloma formed from young or more mature histiocytes, bathing in a fundamental substance, few or abundant in quantity with fine or voluminous collagenous fibers. Vascularization may be slight or serious, the vessels

being often surrounded by a lymphocyte ridge. The main distinguishing feature is the sprinkling of the lesion by myriads of eosinophilia and the absence of malignancy (except in Holle's case with a sarcomatous development).

*The pathogenesis* is highly controversial. Our opinion is that it is not a question of a disorder similar to eosinophilic granuloblastosis of the bones, nor to cutaneous and orificial eosinophilic granuloma, nor to eosinophilic granuloma of the skin and bones, disorders for which Prof. Nanta speaks of a special reticulopathy. In our case, we reiterate, it is a question of an isolated tumor.

It is not a matter of a disorder of allergic origin, for contrary to diffuse granulomatosis, only exceptionally in tumoral eosinophilic granuloblastoma are allergy and eosinophilia of the blood found.

We are of the same opinion as Bolck and Nunès that it depends on a reaction of the "conjunctive" to a local process of irritation (ulcer scar, nearby benign tumor, foreign body e.g; the fragment of sponge in Duroselle's observation).

The important thing is to know that there can be found on the level of the stomach and the ulcer a benign tumor whose clinical and radiological diagnosis is impossible being essentially of an anatomo-pathological order.

Guy Albot

HAAS, ALFRED: *Two cases of advanced carcinoma of the stomach surviving ten years postoperatively*. Am. J. Gastro. 23, 3, 247, March 1955.

Two cases of gastric resection for carcinoma, who have remained without recurrence for nearly ten years, have been presented. The importance of the natural history of cancer is stressed. In tumors which have developed over a period of years and have not yet produced known lymphatic metastases, resection of even very large tumors may prove to be successful. The conclusion which we should draw from such cases is that exploratory laparotomy should be done in every tumor, however large it may be. A very important point is that the resection must be carried out far from the mucosa border of the tumor because of the rapid submucosal spread. When other organs are involved in continuity, they should be resected too. Only metastases to the lymph and blood vessels makes the prognosis hopeless in most cases. Such spread may be detected by careful examination of the supraclavicular glands preoperatively. Palliative resection remains justified.

Franz J. Lust

GALAMBOS, A.: *Congenital anomalies of the duodenum*. Am. J. Gastro. 22, 6, 452. December 1954.

Galambos describes eleven cases of congenital anomalies. The duodenum appeared in somewhat different shape, configuration and position. Practically every case exhibited a design of its own. None of the cases had signs or symptoms referable to this anomaly or to any specific pathology. Their detection was incidental. Association with other congenital anomalies was frequent. The diagnosis was made by roentgenological

demonstration of the abnormality. These abnormalities are rare. Their recognition may be missed, because even if they are demonstrated by the roentgenological examination, they are not necessarily recognized, diagnosed or correctly interpreted.

Franz J. Lust

GALAMBOS, A. AND GALAMBOS, W. M.: *The double gallbladder: A congenital anomaly. Report of nine cases.* Am. J. Gastro. 23, 2, 129. Febr. 1955.

The authors describe nine cases of double gallbladder. All were diagnosed by roentgenography. In the literature extremely few cases are on record and the number of their cholecystographic demonstration is even less. Double gallbladder in the series of the authors was frequently associated with other congenital abnormalities. Its discovery was incidental in each case. There were no clinical signs or symptoms attributable to the presence of this anomaly.

Franz J. Lust

RITTER, SAUL ALFRED AND HAAS, ALFRED: *Mucocele of appendix superimposed on acute suppurative inflammation.* Am. J. Gastro. 23, 2, 124, Febr. 1955.

It is not often possible to make the diagnosis of a mucocele of the appendix preoperatively even if the mass is not very large, especially in the presence of acute infection and with abdominal rigidity. Peritoneoscopy was effectively used by Chaffee and Le Grande to diagnose preoperatively a case of pseudomyxoma peritonei, secondary to a perforated mucocele. All cases of mucocele of the appendix, when not perforated, are curable by appendectomy.

The authors report an unusual case in which there was a mucocele, secondary to chronic inflammation of the appendix, followed by acute gangrenous appendicitis. The patient was cured by appendectomy.

Franz J. Lust

LANGE, L.: *Porcelain gallbladder with carcinoma of the gallbladder.* Fortschr. Roentgenstr. 82, 3, 411. March 1955.

Lange reports the case of a man, 51 years old, who had complaints for only one month. He had lost 7 kg in weight. The roentgenological examination after oral Graham test failed to show a gallbladder. However, there was a round shadow of calcium deposit in the region of the gallbladder. At operation, a porcelain gallbladder was found. The specimen showed the same formation as seen on the roentgenogram. The pathological examination revealed a small scirrhous carcinoma of the gallbladder. It is apparently impossible, to diagnose the carcinoma roentgenologically.

Franz J. Lust

LANGE, L.: *Roentgenological diagnosis of a gallbladder carcinoma with cholecysto-duodenal fistula.* Fortschr. Roentgenstr. 81, 3, 399, Sept. 1954.

Lange describes a case of a 75 year old patient. The stomach was normal. From the duodenal cap a wide opening emptied the barium into the gallbladder. The gallbladder was of irregular outline. Spot films of the region showed the presence of an irregular tumor mass. The autopsy confirmed the diagnosis of a carcinoma of

the gallbladder, which had invaded the duodenum forming a cholecysto-duodenal fistula. The roentgenograms are very instructive.

Franz J. Lust

MUEHLBAUER, MICHAEL A. AND WEISSMANN, EDWARD: *Primary carcinoma of the duodenal bulb.* Am. J. Gastro. 23, 1, 60. Jan. 1955.

A case of primary carcinoma of the duodenal bulb, an exceedingly rare lesion, is described. It is stressed that except for the presence of melana, symptoms of this gastrointestinal lesion occurred late in the disease. Pain was likewise a late sign. The diagnosis was made by radiographic examination. Surgical removal of the tumor was impossible, due to metastatic spread. Microscopically the lesion was described as papillary adenocarcinoma.

Franz J. Lust

ASCTALOS, FERENC AND HORVATH, ISTVAN: *Contribution to the question of the non-acute gastritis phlegmonosa. (Beiträge zur Frage der nicht akut verlaufenden Gastritis phlegmonosa).* Fortschr. Roentgen. 82, 5, May 1955.

A case of a primary and a case of a secondary chronic gastritis phlegmonosa combined with carcinoma are discussed. The primary gastritis phlegmonosa was cured following the administration of antibiotics. The secondary gastritis phlegmonosa combined with a carcinoma was also treated with penicillin, which resulted in a clinical improvement for several months. According to the authors, the treatment had a "scarring" effect on the neoplasm, and a delay in the progress of the neoplastic disease was found.

Franz J. Lust

ALBOT, G., OLIVIER, CL., LIBAUDE, H. AND COUZINET, G.: *Biliary Forms of Duodenal Ulcers.* (Paris)—La Presse Médicale 9, 2, 1955. p. 195.

Long since were the authors interested in the question of biliary forms of duodenal ulcers. This had been the object of their reports in 1950 and 1952. One of them (G. Couzinet) has just published a thesis on 15 personal cases. Results of this work are summarized in the present paper.

1) Under the heading "symptomatic forms" are reported those cases in which the symptomatology is initially ulcerous in its characteristics, which is the commonest type with only a mere vesicular hyperkinesia as "biliary repercussion."

2) Under the heading "complicated forms" are described those cases in which the "biliary feature," on the contrary, is exhibited before the appearance of the duodenal ulcer, this form being more rarely seen.

3) Under the heading "nosographic relationships" is discussed the chronology of the lesions and their interrelation regarding the influence of one upon the other.

4) Finally is considered the question of treatment: whether medical or surgical and which of the lesions, duodenal or biliary, should be dealt with in the first place.

AMER. JOUR. DIG. DIS.

## FURADANTIN

Replying to a question on the accepted treatment of chronic, uncomplicated prostatitis in the Queries and Minor Notes column of the *Journal of the American Medical Association*, 157:1455 (Apr. 16) 1955, a consultant answers that one occasionally sees some rather careful work done using nitrofurantoin (Furadantin, Eaton) in "groups of patients who had been treated for a considerable period of time for chronic, uncomplicated prostatitis." He further advises that the drug be used in conjunction with "sensitivity tests for the specific bacteria found in the nonspecific lesion."

## WYETH PROMOTES THREE TO NEW SALES POSTS

Three members of the Wyeth Laboratories sales staff have been promoted to new positions within the organization, effective immediately it was announced by Stuart V. Smith, vice president of the company.

Lee J. Hymel, Chicago division manager since 1949, has been named assistant sales manager. Donald E. Gilliland succeeds him as division manager of the Cleveland sales area.

Mr. Hymel, a graduate of Soules Business College and the Simon School of Pharmacy, began his business career in 1934 with I. L. Lyons & Co., Ltd., New Orleans wholesale drug firm. In 1943 he joined SMA Corporation as New Orleans sales representative and transferred to Wyeth the following year.

In 1944 he was appointed nutritional detail manager for Wyeth in the New Orleans area and a year later became district sales manager there. He held that position until he was named Chicago division manager six years ago.

Mr. Gilliland entered the drug field 15 years ago as a sales and detail representative for a New York drug manufacturing concern and joined Wyeth in 1945. After serving for two years as the firm's sales representative in St. Louis, he became district manager of the St. Louis area. In 1953 he was promoted to division manager of the Cleveland sales territory, a position he has held since that time.

He is a graduate of Indiana University, where he earned the degree

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of B. S. in Education. For three years following his graduation he was engaged in boys club work in Columbus, Indiana, before turning to the drug business in 1940.

Mr. Main has been Wyeth's district manager in Cleveland for the last seven years. He joined the company in 1936 as a sales representative in Zanesville, Ohio, and later transferred to the Columbus territory before moving on to Cleveland in 1948.

He began a career in pharmacy more than 30 years ago upon graduation from Ohio Northern University. In the late 20's and early 30's he was the owner of a drug store in Ada, Ohio, and later was assistant manager of the Walgreen Drug Company in Columbus and Lima, Ohio, before joining the Wyeth organization.

## PRIZER OFFERS VERSATILE CHEMICAL IN PILOT PLANT QUANTITIES

New York, N.Y., July 18—Acetonedicarboxylic acid, a well-known, highly reactive chemical, was made available today for the first time in pilot plant quantities by Chas. Pfizer & Co., Inc.

Designated by the company as ADA, the compound is derived from fermentation-produced citric acid. A white crystalline powder of high purity, ADA is seen useful industrially for the preparation of pharmaceuticals, insecticides, disinfectants, fungicides, dyestuffs, chelating agents, amino acids, leavening agents and as a synthetic intermediate.

ADA represents another (the seventh) in the company's new series of industrial chemicals made or derived from fermentation. Earlier this year, Pfizer introduced itaconic acid, two itaconic esters, two citric acid ester (Citroflex™) plasticizers and kojic acid as part of its stepped-up industrial chemical program.

In making the announcement, Paul E. Weber, assistant sales manager, Chemical Sales Division, said ADA long has been recognized as a versatile compound and potentially useful intermediate.

"ADA, he said, "is truly a multipurpose molecule. It will react at the carbonyl group, at the carboxyl groups and progressively at the active methylene groups."

In addition, Mr. Weber said, this compound may be condensed with a number of compounds to form oxygen and nitrogen-containing heterocyclics. He declared that, "ADA and its esters, because of their chemical versatility, have long been used as intermediates in the synthesis of complex substances. ADA loses carbon dioxide very readily, a reaction that is accelerated by heating or by acid or alkali."

Weber also noted that ADA's availability had previously been limited because of its instability.

Now, because Pfizer, he said, has developed a high purity form of ADA its stability has been improved both on the shelf and in shipment.

"ADA offers the research chemists a novel synthetic route to the preparation of various drugs," Weber said. He pointed out that as an intermediate ADA can be used in the manufacture of such pharmaceutical compounds as tropinone and atropine, a nerve gas antidote.

According to Weber, ADA should prove especially valuable in the relatively new field of metal chelates. ADA and its esters, he explained, form chelates with copper and iron, and the higher esters of this compound may have use in sequestering heavy metals in fats, oils and petroleum products.

Readily soluble in water and alcohol, ADA has a molecular weight of 146.10 and a melting point of 135° C. (with decomposition).

A comprehensive data sheet and samples are available upon request from the company's Chemical Sales Division, 630 Flushing Avenue, Brooklyn 6, N.Y.

## LAKESIDE BEGINS SYNTHESIZING OWN COMPLEX ORGANIC COMPOUNDS

Milwaukee, Wisc.—Lakeside Laboratories, Inc., has been synthesizing its own complex organic compounds, it was disclosed here by William H. Mohaupt, assistant vice president.

The decision to bring this stage of production into the company's own plant was first made with the development of the series of piperidol drugs, Mr. Mohaupt said. Lakeside has already introduced the first two of these drugs, Dactil and Pipital, indicated respectively for relief



of pain and spasm in the upper gastrointestinal tract and in peptic ulcer.

The development and manufacture of these drugs have necessitated the purchase and installation of process equipment such as high pressure hydrogenation equipment and high vacuum stills, which are now in operation. The equipment will also be used in the development of other series of special compounds.

As part of the company's expand-

ing research activity, and the production of these organic compounds with their intermediates, Lakeside is purchasing more in the heavy chemicals category and moving away from the purchases of fine chemicals, Mr. Mohaupt added.

#### POCKET EDITION OF ELEVEN BLUE MEN PUBLISHED

Twelve stories of medical detection originally written by Berton Roueche for *The New Yorker* have

just been reprinted in pocket book edition entitled "Eleven Blue Men."

First published in hard cover by Little, Brown and Co., Boston, the new Berkley edition of 200,000 includes a report of Mr. Roueche's visit to the laboratories and plant of Chas. Pfizer & Co., Inc. Entitled "Something Extraordinary," this article outlines the company's efforts to unearth and develop antibiotics.

#### STUDY FINDS HYPAAQUE "EXCELLENT" IN UROGRAPHY

The new contrast agent Hypaque is an "excellent urographic substance, with minimal side reactions," Dr. Benedict R. Harrow states in the *Bulletin of the University of Miami School of Medicine*, (9:29, 1955).

Using a 50 per cent solution of Hypaque, manufactured by Winthrop-Stearns Inc., he injected 30 cc. and 60 cc. slowly, by vein, into two different groups of 15 patients. There were no side reactions, with the exception of occasional mild nausea. In addition, the investigator notes, the 60 cc. of Hypaque resulted in x-rays of equal density to those obtained when a higher concentration of another contrast medium was used in a second series of 30 patients.

Although the density of the x-ray views was slightly less on the average with 30 cc. of the 50 per cent Hypaque solution, for routine use it is recommended "as an adequate amount and only for an occasional patient will it be necessary to use larger quantities."

The study also demonstrated that increasing the iodide load does not substantially increase urinary concentration. Other urographic agents tested usually cause a decrease in the pH of the urine, Dr. Harrow says. He adds that Hypaque "almost invariably produced a fairly marked increase in urinary pH."

#### ATTENTION TO NORMAL HEPATIC FUNCTION RECOMMENDED IN TREATMENT OF OBESE PATIENTS

Closer attention to liver function in the treatment of the obese is recommended by a physician here.

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DOUBLE STRENGTH

for indigestion, pain, heartburn, belching, or nausea due to g.i. spasm... the selective spasmolysis of MESOPIN\* (homatropine methylbromide) 1/30 as toxic as atropine, plus the sustained sedation of phenobarbital... with virtual freedom from side effects.

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MESOPIN-PB	Mesopin 2.5 mg. and phenobarbital 15 mg. (yellow)	Mesopin 2.5 mg. and phenobarbital 15 mg. per tsp. (yellow)	
MESOPIN (Double Strength)	5 mg. (white)		
MESOPIN	2.5 mg. (white)	2.5 mg. per tsp. (green)	

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## **XYLOCAINE® VISCOUS** ANTRA

(Brand of lidocaine\*)

the most effective anesthetic

for the proximal parts of the digestive tract



- Quick acting with prolonged effect
- High viscosity and low surface tension permit the anesthetic, Xylocaine Hydrochloride, to come into immediate and intimate contact with the mucous membranes
- Safe . . . nonirritating . . . nonsensitizing.
- Cherry flavored . . . pleasant and easy to take.
- Xylocaine Viscous has proved valuable in the "dumping" syndrome, hiccup, pyloric spasm caused by peptic ulcer, stomatitis, pharyngitis, esophagitis, acute cardiospasm, pylorospasm in infants, severe vomiting of pregnancy, esophagoscopy, gastroscopy, gastric intubation and gastric lavage.
- Contains 2% Xylocaine Hydrochloride in an aqueous solution adjusted to a suitable consistency with carboxymethylcellulose. Cherry flavored for palatability.

Supplied: In bottles of 100 and 450 cc.

Average Dosage: One tablespoonful, administered orally.

Additional information available upon request



Astra Pharmaceutical Products, Inc., Worcester 6, Mass., U.S.A.

\*U.S. Patent No. 2,441,498

He states that it may be more significant than an increased metabolism such as produced by thyroid medication.

Dr. Hyman Sapoznik tried six different formulas on a group of 46 private patients. Five of the six contained amphetamine or a derivative, alone or in combination with thyroid hormone. The sixth, having only small doses of d-Amphetamine and phenobarbital, contained vitamin B<sub>12</sub>, methylcellulose and lipotropic agents as well.

Dr. Sapoznik reports on his study in *The American Journal of Digestive Diseases* (22:159, 1955).

The best reducing combination was the formula containing the lipotropics, which mobilize body fat for metabolic burning. First preparation to contain lipotropics, it is called Obolip (Lakeside Laboratories, Inc.).

"It is revealing that a reducing drug, designed to deal metabolically with the hepatic pathology (fatty

infiltration) associated with obesity, was considerably more successful in aiding weight reduction than agents containing central nervous system stimulants alone or in combination with thyroid preparations," he states.

An average weight loss of three pounds per week during a six-week period of medication was produced during therapy with Obolip. Dr. Sapoznik writes that such a weight loss appears not to be detrimental to the health and well-being of patients.

He adds that almost all the patients on Obolip reported a feeling of relaxation and ease, and all improved in their general attitude.

A number of side effects were noted with the other five formulas.

"The fact that these drugs . . . do not produce the desired results in weight reduction without undesirable side effects, is in contrast to the reasonably uniform and predictable manner in which a reducing agent containing lipotropic agents for the treatment of fatty infiltration of the liver appears to work," Dr. Sapoznik concludes.

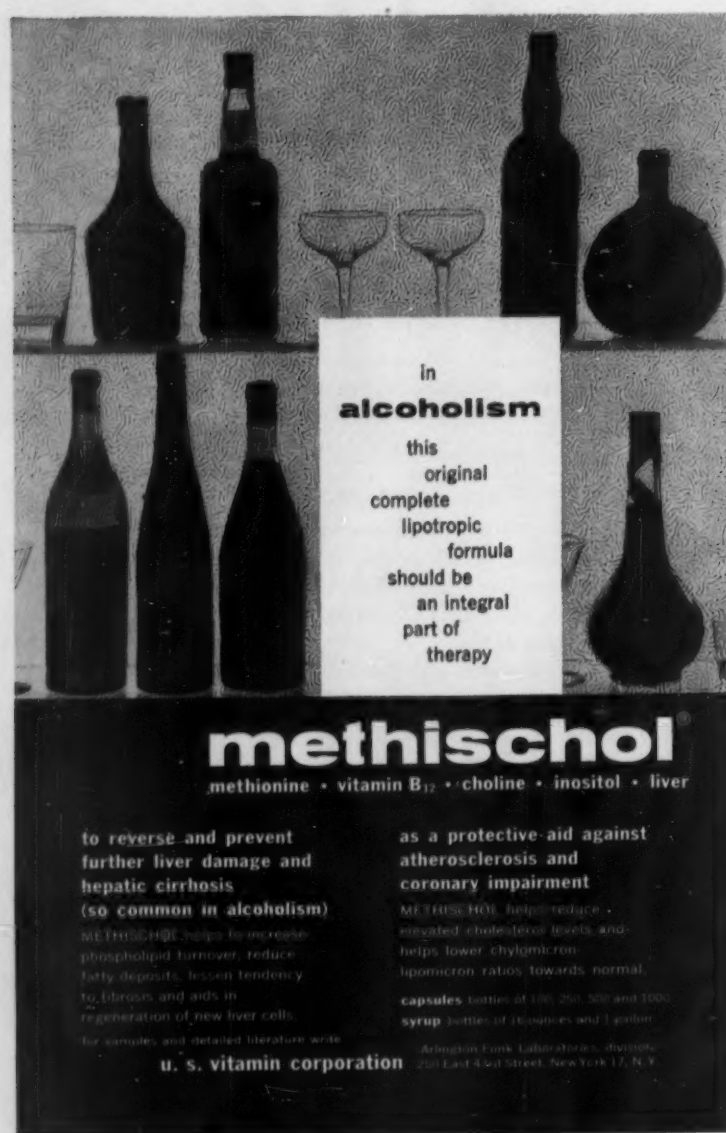
#### EBERBACH'S NEW VARIABLE SPEED ROTATOR MAINTAINS SPEEDS ACCURATELY FOR SEROLOGICAL TESTS

A completely new Variable Speed Rotator by Eberbach for serological tests (V. D. R. L., Kline, Mazzini, etc.) assures constant speed operation at any setting within its range of 100 to 220 r.p.m. in spite of load changes, in line voltage fluctuations and other variables. Speeds selected on the large, calibrated dial are accurate and reproducible.

Built for continuous duty, this rotator also provides timed operation from 0 to 30 minutes. An electric governor accurately maintains operating speed. Slides are held by a sponge rubber pad cemented to the 13" square platform which rotates through a uniform 3/4" diameter circle. Removable 9-place slide carriers are available as accessories.

Complete details in Bulletin 210. Write Eberbach Corporation, Ann Arbor, Michigan.

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to reverse and prevent further liver damage and hepatic cirrhosis (so common in alcoholism)

METHISCHOL helps to increase phospholipid turnover, reduce fatty deposits, lessen tendency to fibrosis and aids in regeneration of new liver cells.

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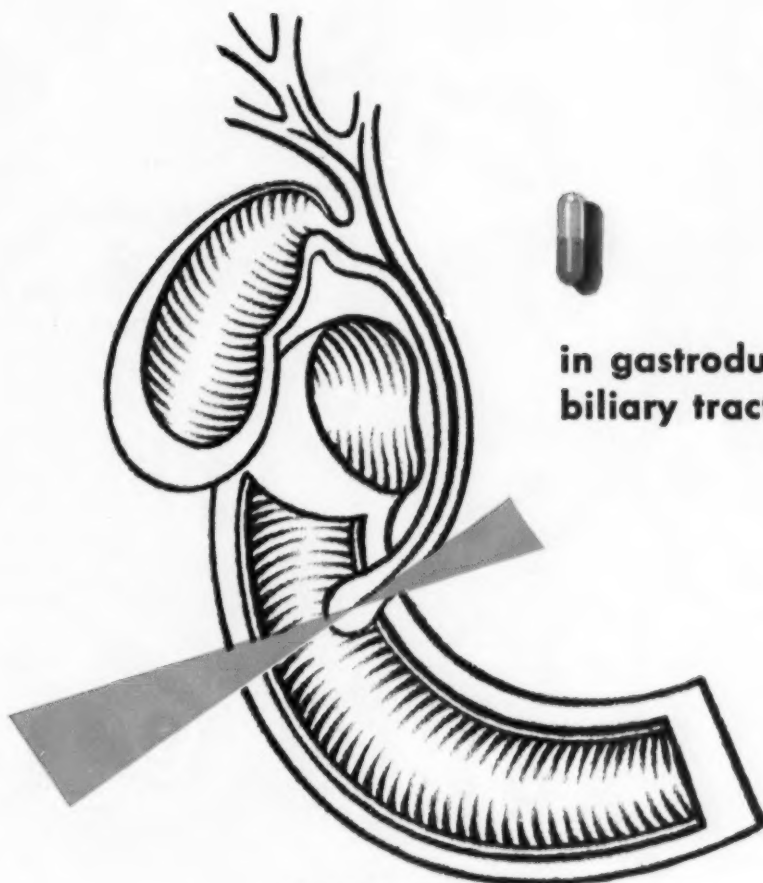
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relieves **pain**  $\Rightarrow$  **spasm** usually in 10 minutes

**prompt** action at the site of visceral pain gives unusually rapid relief

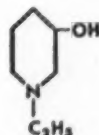
**prolonged** control of spasm gives relief up to four hours

**no interference** with digestive secretions, normal tonus or motility

*L*

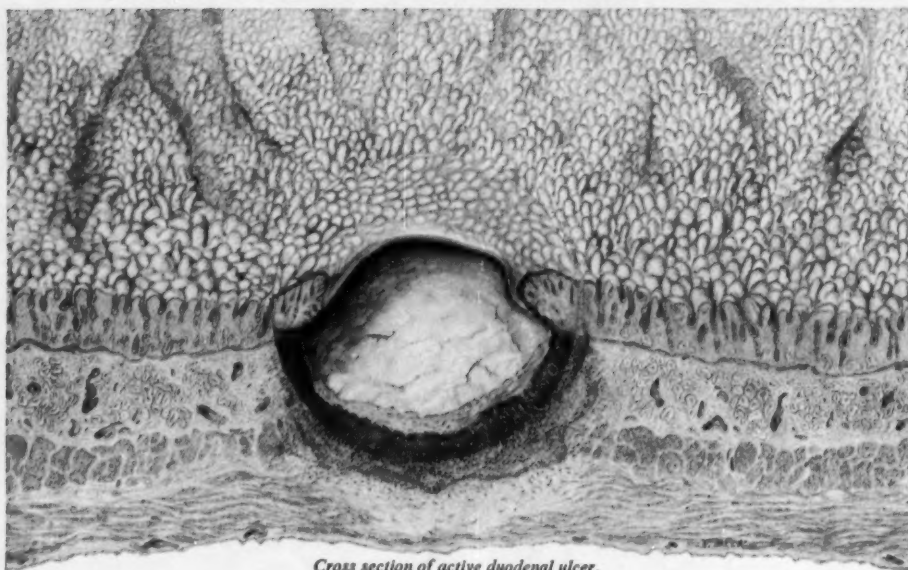
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## PRO-BANTHINE® IN DUODENAL ULCER



Cross section of active duodenal ulcer.

## Dramatic Remission of Ulcer Pain

*Pain of ulcer is associated with hypermotility; the pain is relieved when abnormal motility is controlled by Pro-Banthine.*

"In studying<sup>1</sup> the mechanism of ulcer pain, it is obvious that there are at least two factors which must be considered: namely, hydrochloric acid and motility.

"... our studies indicate that ulcer pain in the uncomplicated case is invariably associated with abnormal motility....

"Prompt relief of ulcer pain by ganglionic blocking agents... coincided exactly with cessation of abnormal motility and relaxation of the stomach."

Pro-Banthine Bromide ( $\beta$ -diisopropylaminoethyl xanthene-9-carboxylate methobromide, brand of propantheline bromide) is a new, improved, well tolerated anticholinergic agent which consistently reduces hypermotility of the stomach and intestinal tract. In peptic ulcer therapy<sup>2</sup> Pro-Banthine has brought about dramatic remissions, based on roentgenologic evidence. Concurrently there is a reduction of pain, or in many instances, the pain and discomfort disappear early in the program of therapy.

One of the typical cases cited by the authors<sup>2</sup> is that of a male patient who refused surgery despite the presence of a huge crater in the duodenal bulb.

"This ulcer crater was unusually large, yet on 30 mg. doses of Pro-Banthine [q.i.d.] his symptoms were relieved in 48 hours and a most dramatic diminution in the size of the crater was evident within 12 days."

Pro-Banthine is proving equally effective in the relief of hypermotility of the large and small bowel, certain forms of pylorospasm, pancreatitis and ureteral and bladder spasm. G. D. Searle & Co., Research in the Service of Medicine.

1. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, *Gastroenterology* 23:252 (Feb.) 1953.

2. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, *Gastroenterology* 25:416 (Nov.) 1953.

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